PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 401/04, 401/14, 405/14, 405/12, 401/12, A61K 31/445, 31/435

A1

(11) International Publication Number: WO 98/04545

(43) International Publication Date: 5 February 1998 (05.02.98)

(21) International Application Number: PCT/US97/12923

(22) International Filing Date: 29 July 1997 (29.07.97)

(30) Priority Data:
08/690,522 31 July 1996 (31.07.96) US

(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(72) Inventors: COOPER, Alan, B.; 23 Natalie Drive, West Caldwell, NJ 07006 (US). WANG, James, J.-S.; 47 Unami Terrace, Westfield, NJ 07090 (US). LOVEY, Raymond, G.; 65 Woodside Avenue, West Caldwell, NJ 07006 (US). DESAI, Jagdish, A.; 3 Forest Park Terrace, Spotswood, NJ 08884 (US). SAKSENA, Anil, K.; 53 Beverley Road, Upper Montclair, NJ 07043 (US). GIRIJAVALLABHAN, Viyyoor, M.; 10 Maplewood Drive, Parsippany, NJ 07054 (US). DOLL, Ronald, J.; 126 Union Avenue, Maplewood, NJ 07040 (US).

(74) Agents: MAJKA, Joseph, T. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL TRICYCLIC N-CYANOIMINES USEFUL AS INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

Novel tricyclic N-cyanoimine compounds and pharmaceutical compositions are disclosed which are inhibitors of the enzyme, farnesyl-protein transferase. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering the novel tricyclic N-cyanoimines compound to a biological system. In particular, the method inhibits the abnormal growth of cells in mammals such as a human.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL TRICYCLIC N-CYANOIMINES USEFUL AS INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND

Patent application WO 95/00497 published 5 January 1995 under the Patent Cooperation Treaty (PCT) describes compounds which inhibit the enzyme, farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be additional compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

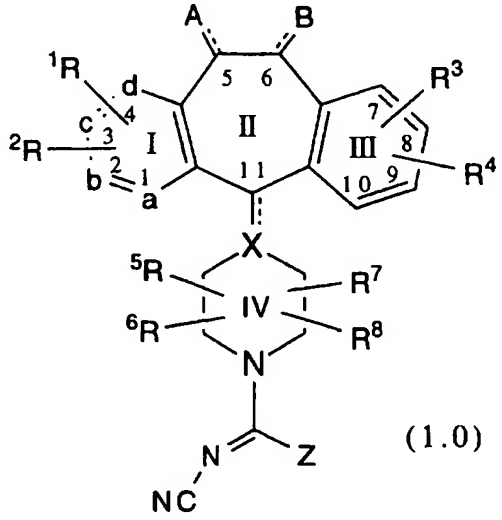
SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a

geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. Several compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

Compounds useful in the claimed methods are represented by Formula 1.0:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2; each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$ (e.g., $-OCH_3$), $-COR^{10}$, $-SR^{10}$ (e.g., $-SCH_3$ and $-SCH_2C_6H_5$), $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2, e.g., $-SOCH_3$ and $-SO_2CH_3$), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$,

$-SR^{11}C(O)OR^{11}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{11}N(R^{75})_2$ wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$ (e.g., $-S(CH_2)_2NHC(O)O$-t-butyl and $-S(CH_2)_2NH_2$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} and R^{12} independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, aryl, aralkyl or $-NR^{40}R^{42}$ wherein R^{40} and R^{42} independently represent H, aryl, alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl;

R^{11} represents alkyl or aryl;

X represents N, CH or C, such that when X is N or CH, there is a single bond to carbon atom 11 as represented by the solid line; or when X is C, there is a double bond to carbon atom 11, as represented by the solid and dotted lines;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-NO_2$, $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, oxy, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4; and

Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, -OR^{40}, -SR^{40}, -$CR^{40}R^{42}$ or -$NR^{40}R^{42}$ wherein R^{40} and R^{42} are defined hereinbefore.

Preferably in compound (1.0), there is a single bond at carbon atom 11, X is carbon, positions 3, 8 and 10 are substituted on the ring, preferably with halo; and Z is -NHR^{40}, preferably where R^{40} is heteroarylalkyl, more preferably 3 or 4-methyl pyridyl N-oxide.

In another embodiment, the present invention is directed toward a pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound (1.0) in combination with a pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed toward a method for inhibiting the abnormal growth of cells, including transformed cells, comprising administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs, and (4) benign or malignant cells that are activated by mechanisms other than the Ras protein. Without wishing to be bound by theory, it is believed that these compounds may function either through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer, or through inhibition of ras farnesyl protein transferase, thus making them useful for their antiproliferative activity against ras transformed cells.

The cells to be inhibited can be tumor cells expressing an activated ras oncogene. For example, the types of cells that may be inhibited include pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells. Also, the inhibition of the abnormal growth of cells by the treatment with compound (1.0) may be by inhibiting ras farnesyl protein transferase. The inhibition may be of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

Alternatively, compounds (1.0) may inhibit tumor cells activated by a protein other than the Ras protein.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein.

In another embodiment, the present invention is directed toward a method for inhibiting ras farnesyl protein transferase and the farnesylation of the oncogene protein Ras by administering an effective amount of compound (1.0) to mammals, especially humans. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

M^+ -represents the molecular ion of the molecule in the mass spectrum;

MH^+ -represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

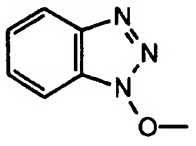
Bu-represents butyl;

Et-represents ethyl;

Me-represents methyl;

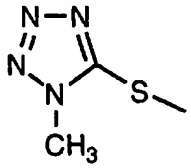
Ph-represents phenyl;

benzotriazol-1-yloxy represents



;

1-methyl-tetrazol-5-ylthio represents



;

alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms; for example methyl, ethyl, propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; wherein said alkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy (=O), phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

alkoxy-an alkyl moiety of one to 20 carbon atoms covalently bonded to an adjacent structural element through an oxygen atom, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like; wherein said alkoxy group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms; wherein said alkenyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms; wherein said alkynyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

aryl (including the aryl portion of aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is phenyl), wherein said aryl group optionally can be fused with aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the available substitutable carbon and nitrogen atoms in said aryl group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

aralkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more aryl groups; wherein said aralkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$; Representative aralkyl groups include benzyl and diphenylmethyl;

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms; wherein said cycloalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

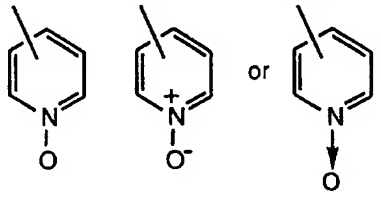
cycloalkylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more cycloalkyl groups; wherein said cycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

halo-represents fluoro, chloro, bromo and iodo;

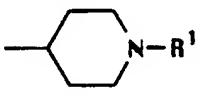
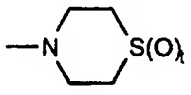
heteroalkyl-represents straight and branched carbon chains containing from one to twenty carbon atoms, preferably one to six carbon atoms interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N-; wherein any of the available substitutable carbon and nitrogen atoms in said heteroalkyl chain may be optionally and independendently substituted with one, two, three or more of the following: halo, C_1-C_6 alkyl, aryl, cyano, hydroxy, alkoxy, oxy, phenoxy, $-CF_3$, $-OCF_3$, amino, alkylamino, dialkylamino, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, or $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

heteroaryl-represents cyclic groups having at least one heteroatom selected from O, S and N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups containing from 2 to 14 carbon atoms,wherein said heteroaryl group optionally can be fused with one or more aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the available substitutable carbon or nitrogen atoms in said heteroaryl group and/or said fused ring(s) may be optionally and independendently substituted with one, two, three or more of the following: halo, C_1-C_6 alkyl, aryl, cyano, hydroxy, alkoxy, oxy, phenoxy, $-CF_3$, $-OCF_3$, amino, alkylamino, dialkylamino,

heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, or $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$. Representative heteroaryl groups can include, for example, furanyl, imidazoyl, pyrimidinyl, triazolyl, 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl N-oxide wherein pyridyl N-oxide can be represented as:



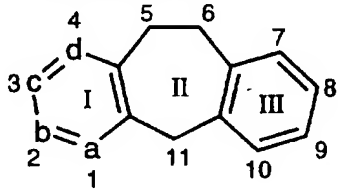
heteroarylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heteroaryl groups; wherein said heteroarylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$; as exemplified by 2-, 3- or 4-pyridylmethyl or 2-, 3- or 4-pyridylmethyl N-oxide;

heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N- , wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein any of the available substitutable carbon and nitrogen atoms in the ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$. Representative heterocycloalkyl groups can include 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 1-, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 1-, 2- or 3-piperizinyl, 2- or 4-dioxanyl, morpholinyl,  or  wherein R^1 is defined hereinbefore and t is 0, 1 or 2.

heterocycloalkylalkyl- represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heterocycloalkyl groups; wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein said heterocycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$.

The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et_3N); diethyl ether (Et_2O); ethyl chloroformate ($ClCO_2Et$); and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC).

Reference to the position of the substituents R^1, R^2, R^3, and R^4 is based on the numbered ring structure:



Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers and diastereoisomers) . The invention contemplates all such stereoisomers both in pure form and in mixture, including racemic mixtures. For example, the carbon atom at the C-11 position can be in the S or R stereoconfiguration.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

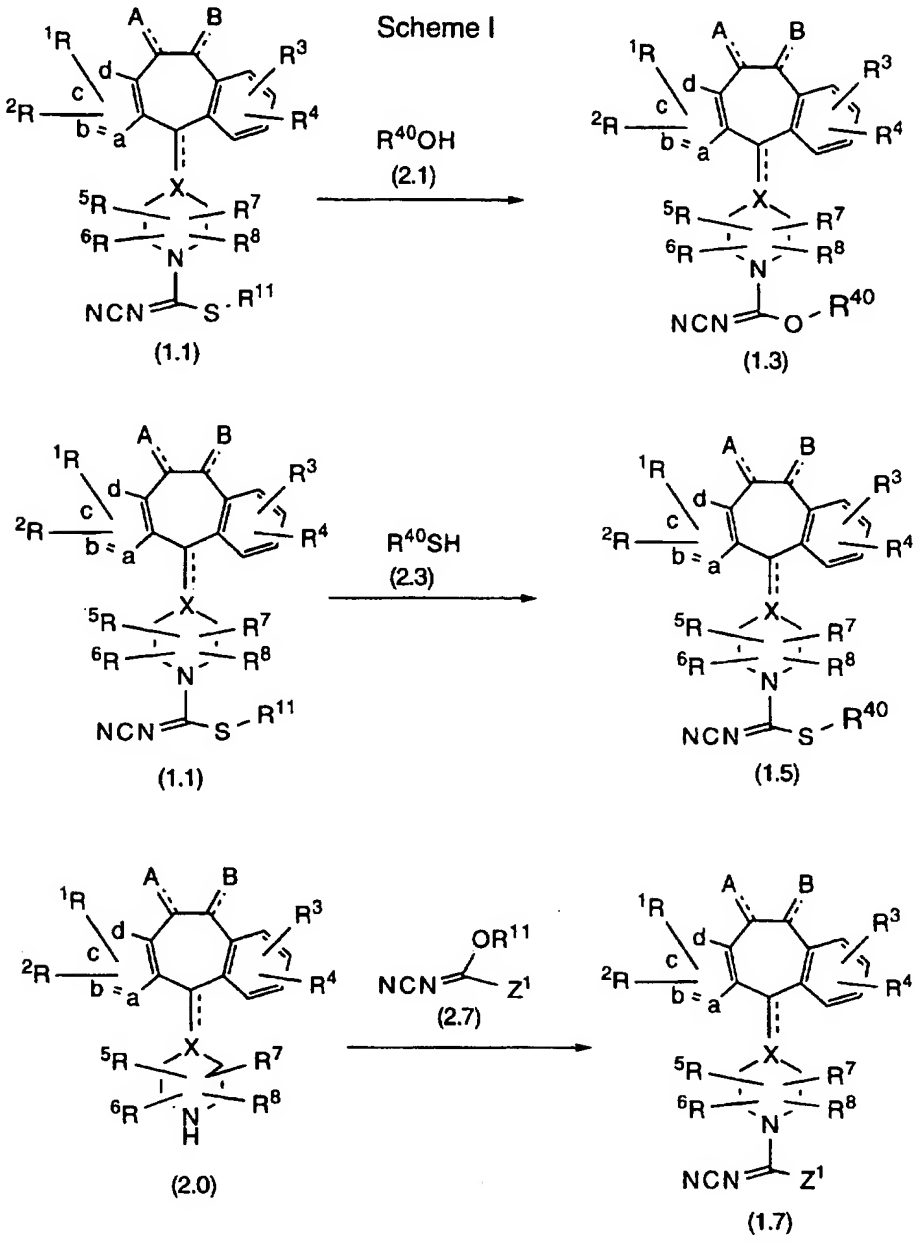
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purpopses of the invention.

Compounds of the invention may be made by the methods described in the examples below, and by the methods described in WO 95/10516 published April 20, 1995--see, for example, the methods for preparing compounds of Formula 400.00.

On page 57 at lines 7 to 16 of WO 95/10516 a process is disclosed for introducing substituents at the C-3 position of pyridine Ring I of Formula 1.0 by nitrating a compound of Formula 415.00. The nitro group may then be reduced to the corresponding amine using the disclosed reagents or powdered Zn and either $CuCl_2$ or $CuBr_2$ in aqueous EtOH .

Compounds of the present invention can be prepared according to the following Scheme I:

Scheme I



wherein Z^1 represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl and $-CR^{40}R^{42}$; the dotted line represents a single or double bond; and a, b, c, d, A, B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^8, R^{11}, R^{40} and R^{42} are as defined hereinbefore.

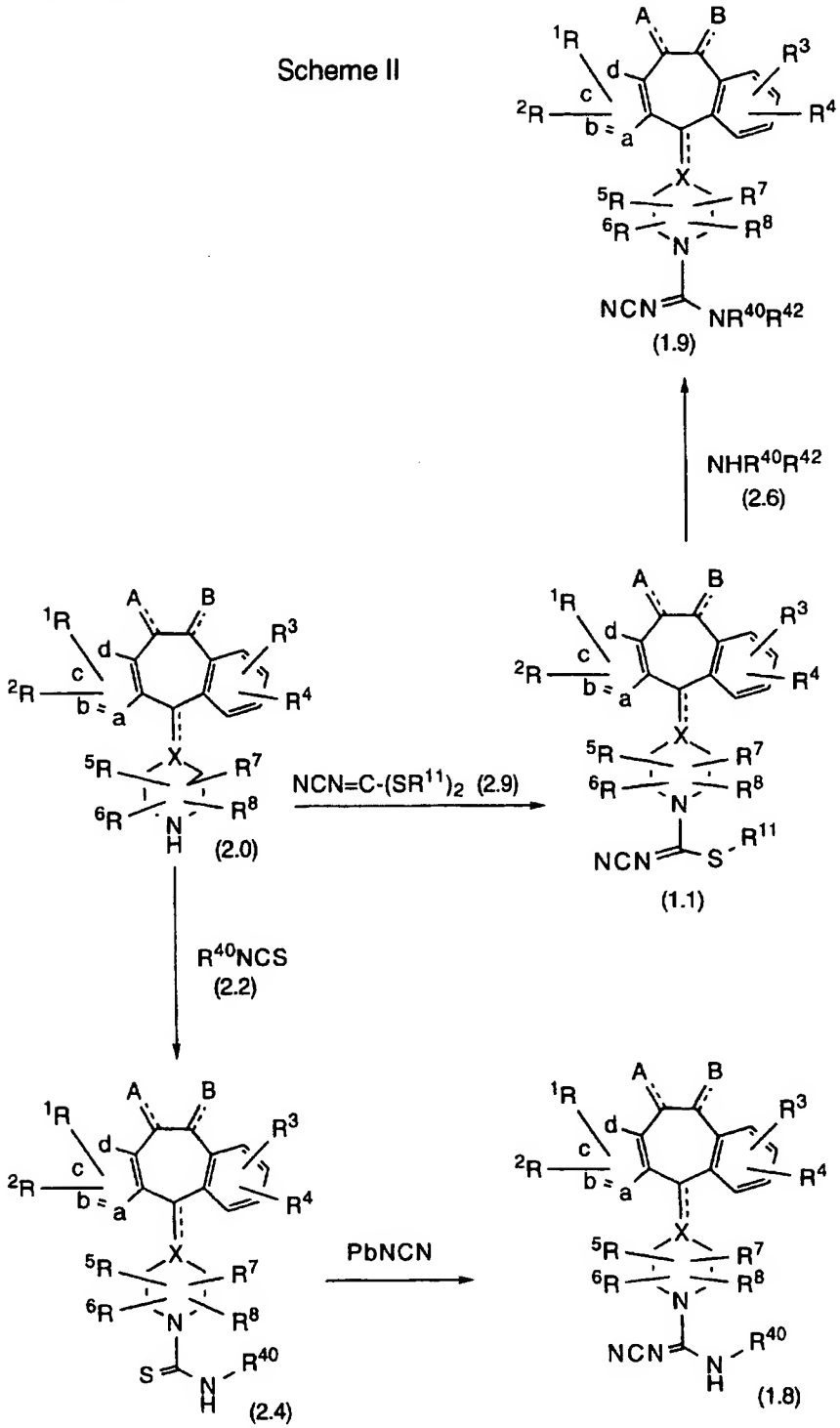
Referring to the Scheme I, compounds of formula (1.3) can be prepared by reacting the compounds of formula (1.1), preferably where R^{11} is alkyl such as methyl, with alcohol ($R^{40}OH$) of formula (2.1) in the presence of a suitable base, and optional non-protic solvent, in amounts and under conditions effective to give compounds (1.3). Suitable bases include organic bases such as pyridine and triethylamine; or inorganic bases of alkali and alkaline earth metals including carbonates such as sodium, lithium, potassium and cesium carbonates, hydroxides such as sodium and potassium hydroxides; hydrides such as sodium or potassium hydride; and sodium t-butoxide, preferably sodium hydride. Suitable non-protic solvents include ethers, dimethyformamide (DMF), dimethylsulfoxide (DMSO), tetrahydrofuran (THF), dimethoxyethane (DME) and mixtures thereof, preferably DMF. Alternatively, the reaction can be carried out neat, using an excess of the alcohol. The amounts of alcohol (2.1) can range from about 1 to about 10 moles per mole of compound (1.1). Temperatures can range from 0° to 100°C, or reflux of the reaction mixture.

Compounds of formula (1.5) can be prepared by reacting the compounds of formula (1.1) with thiol ($R^{40}SH$) of formula (1.1) in the presence of a suitable base, and optional non-protic solvent to give compounds (1.5), using reaction conditions as described for preparing compounds (1.3), above.

Compounds of formula (1.7) can be prepared by reacting the compounds of formula (2.0) with N-cyanaoimidate of formula (2.7) in the presence of an optional non-protic solvent to give compounds (1.7), using reaction conditions as described for preparing compounds (1.3), above.

Compounds of the present invention can be prepared according to the following Scheme II:

Scheme II



wherein a, b, c, d, A, B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^8, R^{11}, R^{40} and R^{42} are as defined hereinbefore; and the dotted line represents a single or double bond..

Referring to the Scheme II, compounds of formula (1.1) can be prepared by reacting the compounds of formula (2.0) with N-cyanodithioiminocarbonate (NCN=C-$(SR^{11})_2$ of formula (2.9) in the presence of a suitable protic or non-protic solvent, in amounts and under conditions effective to give compounds (1.1). Suitable protic solvents include C_{1-10} alkanols, such as methanol, ethanol, propanol, hexanol, octanol, decanol and the like. Suitable non-protic solvents are described hereinbefore. The amounts of N-cyanodithioiminocarbonate (2.9) can range from about 1 to about 10 moles per mole of compound (2.0). Temperatures can range from 0° to 100°C, or reflux of the reaction mixture.

Compounds of formula (1.9) can be prepared by reacting the compounds of formula (1.1) with amine ($NHR^{40}R^{42}$) of formula (2.6) with an optional base and/or optional protic or aprotic solvent such as those described hereinbefore. In a first procedure, compound (1.1) is reacted with amine (2.6) neat, at temperatures ranging from about 50° to 80°C. In a second procedure, compound (1.1) is reacted with about equimolar amounts of amine (2.6) in the presence of a base such as sodium hydride and an aprotic solvent such as DMSO or DMF. In a third procedure, compound (1.1) is reacted with excess amine (2.6) in an protic solvent such as ethanol. In a fourth procedure, compound (1.1) is reacted with amine (2.6) neat, using catalytic amounts of base, such as sodium hydride. In a fifth procedure, compound (1.1) is reacted with greater than two equivalents of amine (2.6) in an aprotic solvent such as DMF at a temperature of about 75°C. Except as noted otherwise, temperatures can range from 0° to 100°C, or reflux of the reaction mixture and amounts of amine (2.6) can range from 1 to about 10 moles per mole of compound (1.1).

Compounds of formula (2.4) can be prepared by reacting the compounds of formula (2.0) with isothiocyanate ($R^{40}NCS$) of formula (2.2) in the presence of a suitable non-protic solvent in amounts and under conditions effective to give compounds (2.4). Suitable non-protic solvents are described hereinbefore. The amounts of isothiocyanate (2.2) can range from about 1 to about 10 moles per mole of compound (2.0).

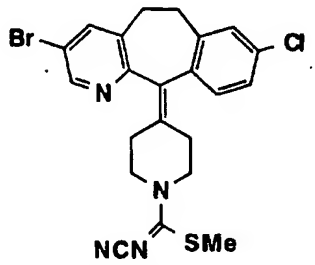
Temperatures can range from 0° to 100°C, or reflux of the reaction mixture.

Compounds of formula (1.8) can be prepared by reacting the compounds of formula (2.4) with lead cyanamine (PbNCN) in the presence of a suitable non-protic solvent in amounts and under conditions effective to give compounds (2.4). Suitable non-protic solvents are described hereinbefore, preferably DMF. The amounts of lead cyanamine can range from about 1 to about 10 moles per mole of compound (2.4). Temperatures can range from 0° to 100°C, or reflux of the reaction mixture.

Compound of fomula 1.0 can be isolated from the reaction mixture using conventional procedures, such as, for example, extraction of the reaction mixture from water with organic solvents, evaporation of the organic solvents, followed by chromatography on silica gel or other suitable chromatographic media.

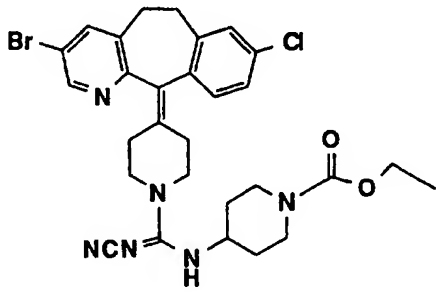
Compounds of the present invention and preparative starting materials therof, are exemplified by the following examples, which should not be construed as limiting the scope of the disclosure.

Example 1. Methyl 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-B-cyano-1-piperidinecarboximidothioate



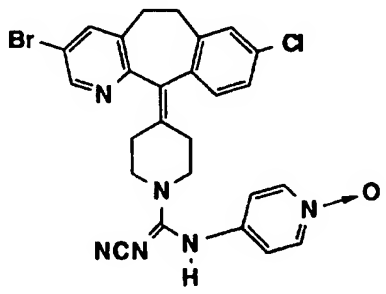
Dissolve 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine (40 gm, 0.1 mol) in 600 mL of absolute ethanol. Add dimethyl N-cyanodithioiminocarbonate (16.5 gm, 0.11 mol) and reflux under a dry nitrogen atmosphere for two hours. Evaporate to dryness to obtain a brown foamy solid. Chromatograph on silica gel using 25% to 50% ethylacetate/hexanes as the eluent to obtain 50.8 gm of title compound. FABMS M+1= 489

Example 2. Ethyl 4-[[[4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinyl](cyanoimino)methyl]amino]-1-piperidinecarboxylate



Dissolve methyl 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-B-cyano-1-piperidinecarboximidothioate (0.1 gm, 0.20 mmol) in 1 ml of ethyl 4-amino-1-piperidinecarboxylate. Stir at 100 °C for 18 hours. Let cool to room temperature. Add the mixture to water and filter the resulting solids. Dissolve the solid in methylene chloride and chromatograph on silica gel using 5% methanol/methylene chloride as eluent to obtain 0.15 gm (34%) of title product. FABMS M+1= 613

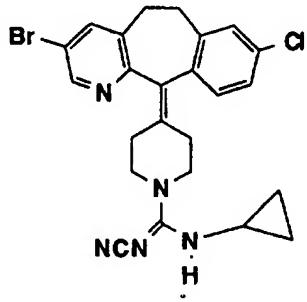
Example 3. [[4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinyl](4-pyridinylamino)methylene]cyanamide N1-oxide



Dissolve methyl 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-B-cyano-1-piperidinecarboximidothioate (0.3 g, 0.60 mmole) and 4-aminopyridyl-N-

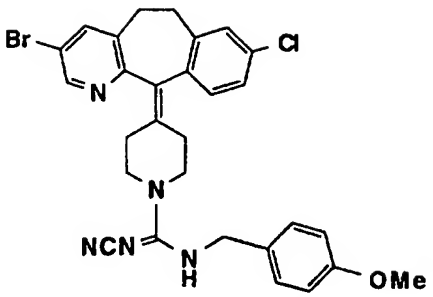
oxide (0.07 gm, 0.60 mmol) in 5 mL of dimethylsulfoxide under a dry nitrogen atmosphere at ambient temperature. Add sodium hydride as a 60% oil dispersion (24 mg,0.6 mmol) portionwise while stirring. After stirring 2 hours, add the reaction mixture to brine and extract with 20 mL of methylene chloride three times. Combine the extracts, dry over magnesium sulfate, filter and evaporate to an oil. Chromatograph the oil on a silica gel coloumn using 2% to 10% methanol in methylene chloride to obtain 0.15 g (47%) of title compound as a solid. FABMS M+1=549.1

Example 4. [[4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinyl][cyclopropylamino]methylene] cyanamide



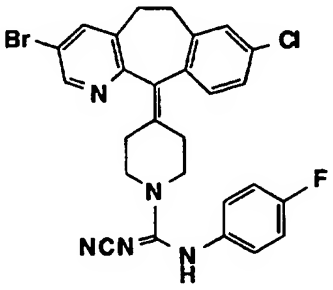
Dissolve methyl 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-B-cyano-1-piperidinecarboximidothioate (0.15 gm, 0.31 mmol) in 3 mL of absolute ethanol. Add cyclopropylamine (0.3 mL, 4.30 mmol) and stir at ambient temperature. After 24 hours , add the reaction mixture to brine and extract with 20 mL of methylene chloride three times. Combine the extracts, dry over magnesium sulfate, filter and evaporate to an oil. Chromatograph the oil on a silica gel coloumn using 2% to 10% methanol in methylene chloride to obtain 0.133 gm (86%) of the title compound as a solid. FABMS M+1= 498.

Example 5. [[4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinyl[[(4-methoxyphenyl)methyl] amino] methylene] cyanamide



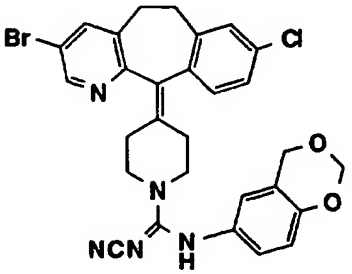
Dissolve methyl 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-B-cyano-1-piperidinecarboximidothioate (0.5 gm, 1.02 mmol) in 5 mL of DMF. Add 4-methoxybenzylamine (0.4 mL, 2.9 mmol) and stir at 75 °C for 24 hours. Add to brine and extract with ethyl acetate three times. Dry the extract over magnesium sulfate, filter, and evaporate to dryness. Chromatograph on silica gel using 5% methanol/methylene chloride as eluent to obtain 0.4 gm, (68%) of title compound. FABMS M+1= 578

Example 6. [[4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinyl] [(4-fluorophenyl)amino]methylene]cyanamide



Dissolve methyl 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-B-cyano-1-piperidinecarboximidothioate (0.25 gm, 0.51 mmol) in 2.5 mL of 4-fluoroanaline. While sitrring under a dry nitrogen atmosphere add approximately 10 mg of sodium hydride and stir at 100 °C for 1 hr. Let cool to room temperature. Add to brine and extract with ethyl acetate three times. Dry the extract over magnesium sulfate, filter, and evaporate to dryness and chromatograph on silica gel using 5% methanol/methylene chloride as eluent to obtain 0.155 gm (55%) of title compound. FABMS M+1= 552.

Example 7. [[(4H-1,3-benzodioxin-6-yl) amino] [4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinyl] methylene] cyanamide



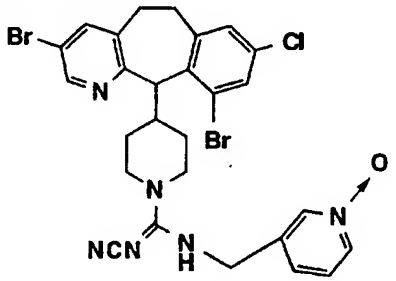
Dissolve 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-N-(4H-1,3-benzodioxin-6-yl)-1-piperidinecarbothioamide (0.1 gm, 0.198 mmol) in dry N,N-dimethylformamide (DMF). Add lead cyanamide (98 mg, 0.39 mmol) and benzyltriethylammonium chloride (5 mg) and stir at 90 °C for 2 days.). Add lead cyanamide (98 mg, 0.39 mmol) and benzyltriethylammonium chloride (5 mg) again and sitr for 24 hrs. Add to brine and extract with ethyl acetate three times. Dry the extract over magnesium sulfate, filter, and evaporate to dryness. Chromatograph on silica gel using 5% methanol/methylene chloride as eluent to obtain 39 mg (38%) of title compound. FABMS M+1= 701

Example 8. [[4-(3, 10-dibromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinyl](3-pyridyinyl)methylene]cyanamide

Dissolve 4-(3,10-dibromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine (0.2 gm, 0.43 mmol) in 2 mL of DMF. Add isopropyl-N-cyano-3-pyridylimidate [ref:

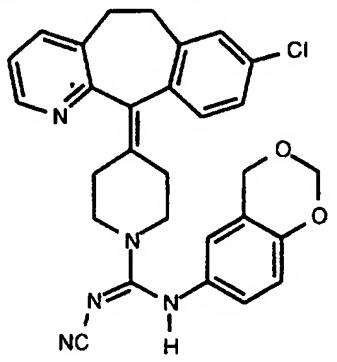
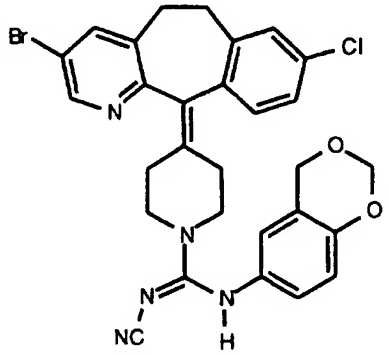
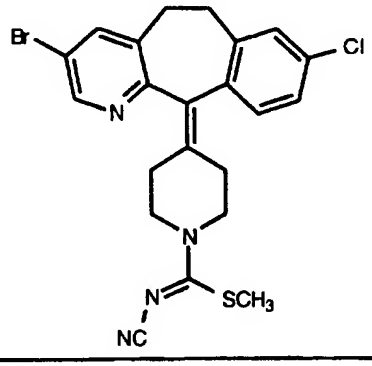
Chem. Pharm. Bull. 42(12) 2475 (1994)] (0.16gm, 0.86 mmol) and stir at 75 °C for 24 hours. Add to brine and extract with ethyl acetate three times. Dry the extract over magnesium sulfate, filter, and evaporate to dryness. Chromatograph on silica gel using 5% methanol/methylene chloride as eluent to obtain 0.16 gm of title compound. FABMS M+1=599.

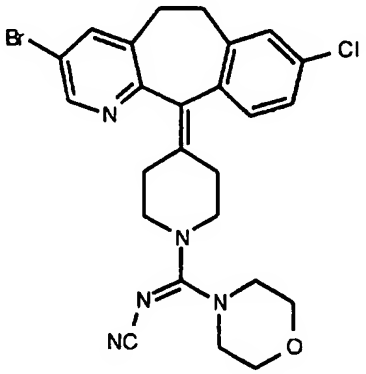
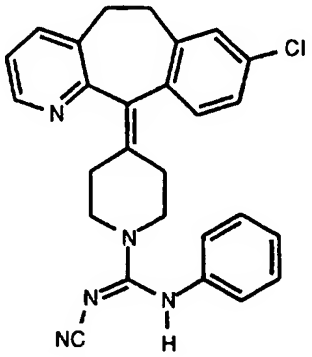
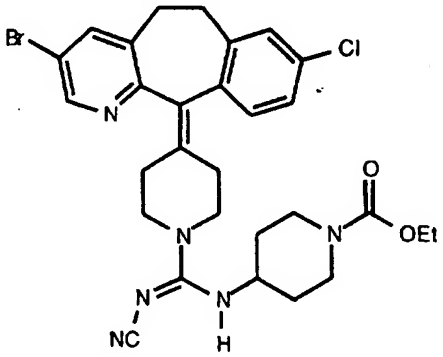
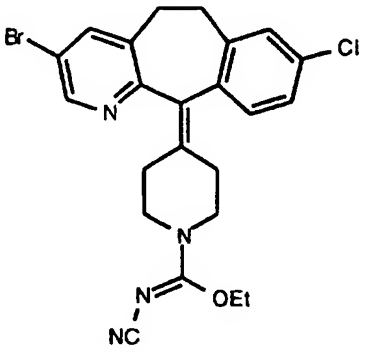
Example 9. N-cyano-4-(3,10-dibromo-8-chloro-6,11-dihydro-5h-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-n'-(3-pyridinylmethyl)-1-piperidinecarboximidamide n1-oxide

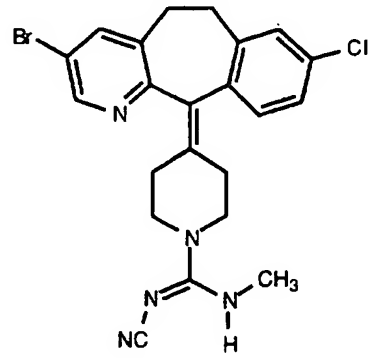
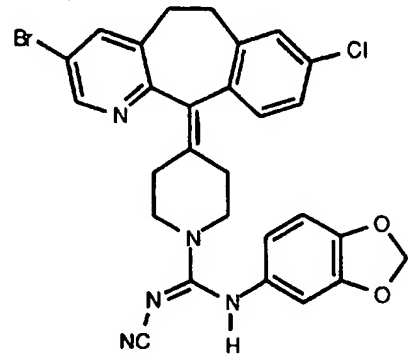
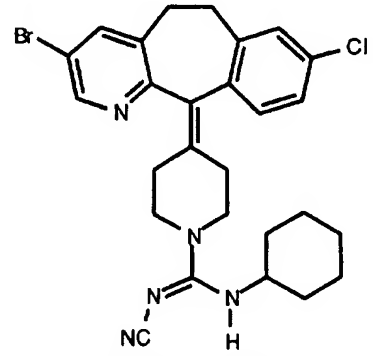
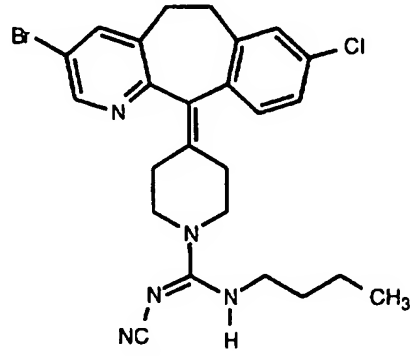


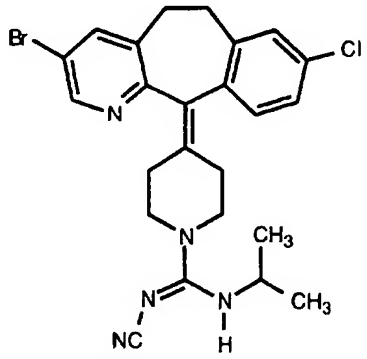
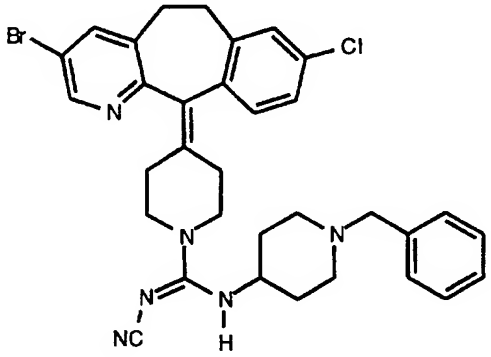
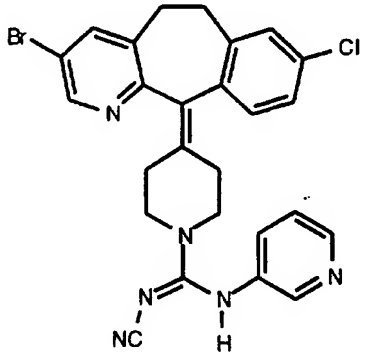
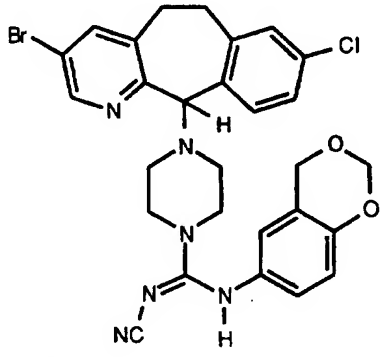
Dissolve methyl 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-B-cyano-1-piperidinecarboximidothioate (1.0 g, 1.76 mmole) and 3-aminomethylpyridyl-N-oxide (0..65 gm, 5.8 mmol) in 10 mL of N,N-dimethylformamide under a dry nitrogen atmosphere at 135 °C while stirring. After stirring 2 hours, add the reaction mixture to brine and extract with 20 mL of methylene chloride three times. Combine the extracts, dry over magnesium sulfate, filter and evaporate to an oil. Chromatograph the oil on a silica gel coloumn using 2% to 10% methanol in methylene chloride to obtain 0.23 g of title compound as a solid. FABMS M+1=563

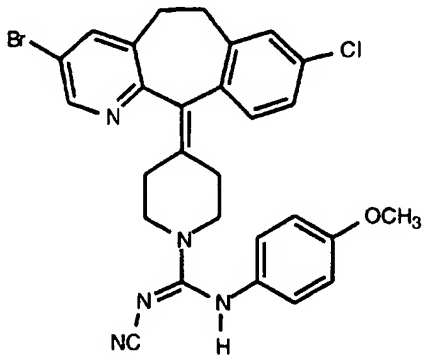
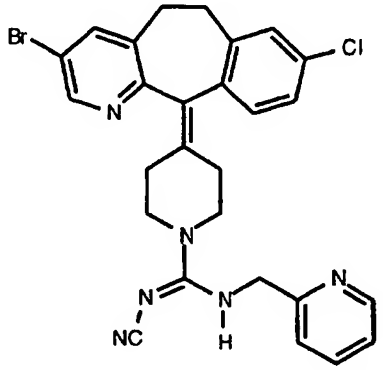
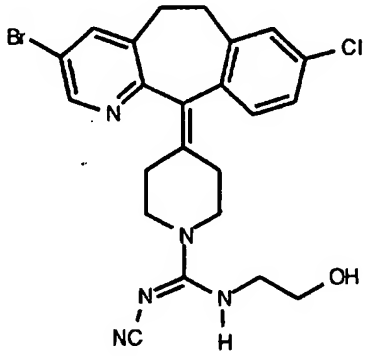
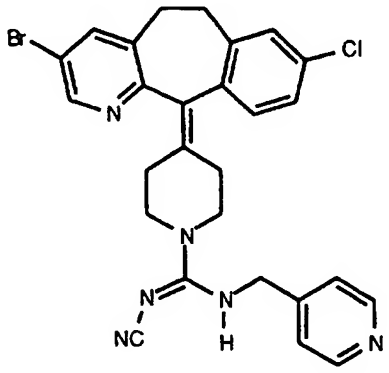
Using the processes described above and substituting appropriate reagents, the compounds described in the following table are prepared.

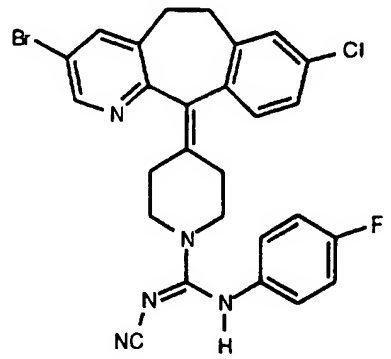
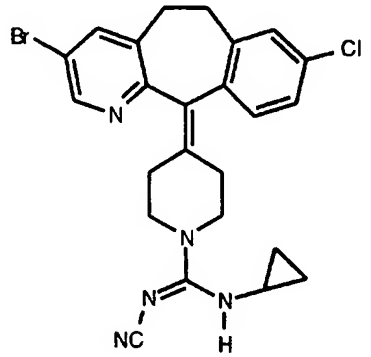
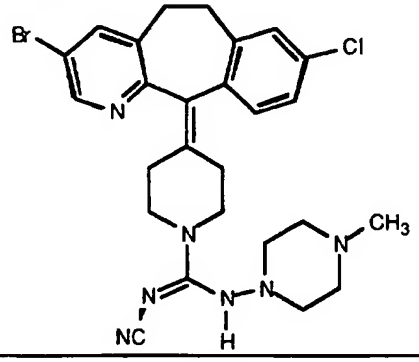
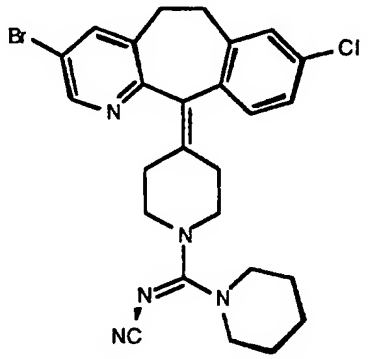
Example No.	Product Compound	FPT IC_{50} (uM)	COS IC_{50} (uM)
10		0.018	0.25
11		0.015	0.25
12		<0.41	

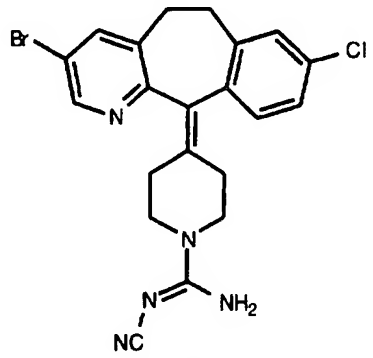
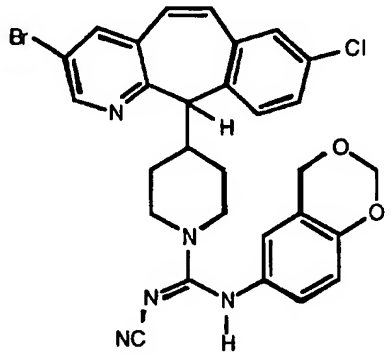
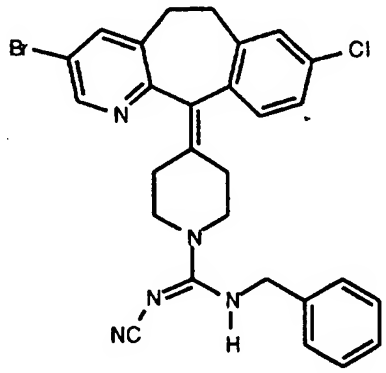
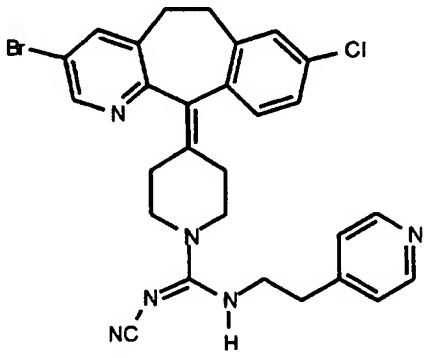
13		0.72	
14		0.086	2.5
15		0.042	0.56
16		0.054	2.3

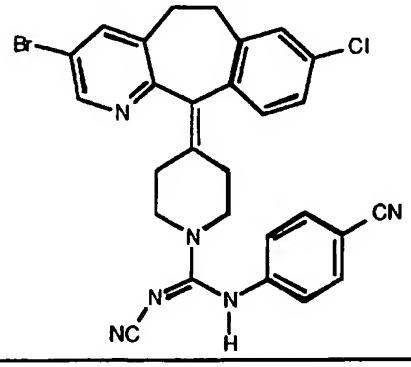
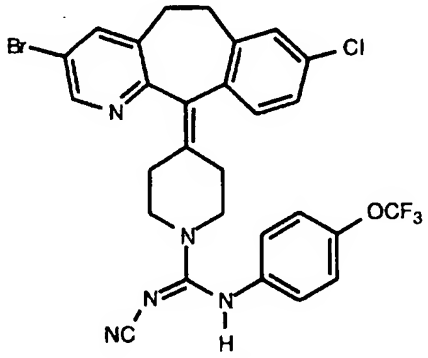
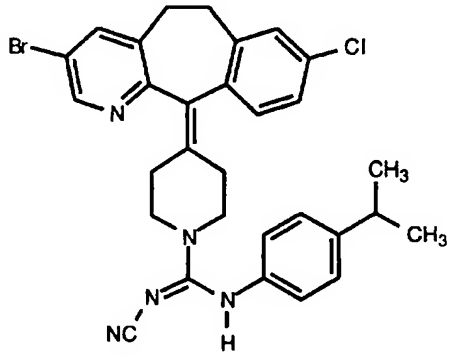
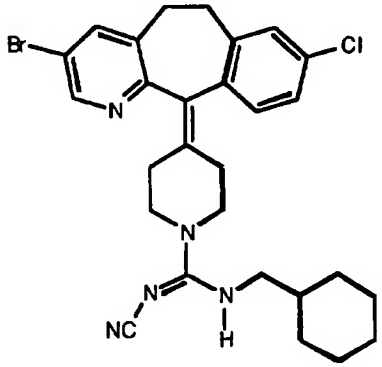
17		0.26	5.0
18		0.038	0.8
19		0.020	0.48
20		0.105	1.6

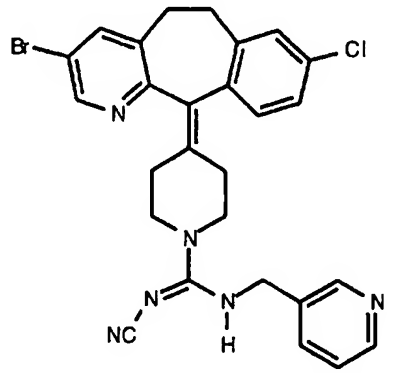
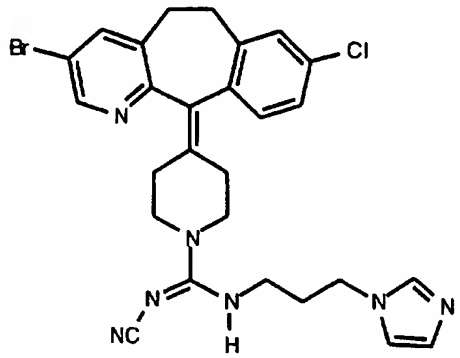
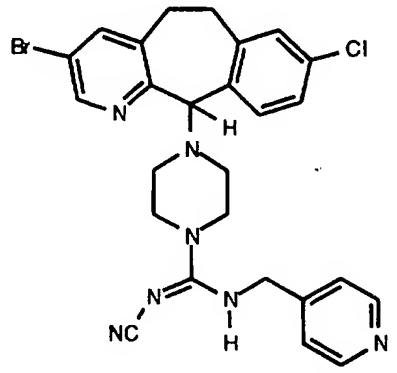
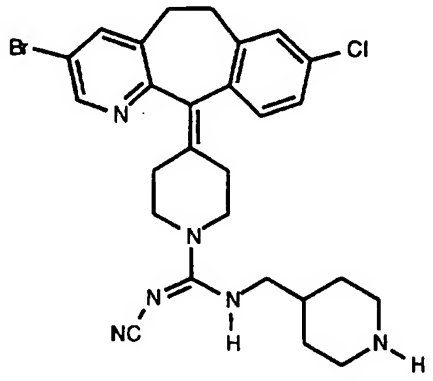
21		0.124	
22		0.17	
23		0.14	2.4
24		0.010	<0.25

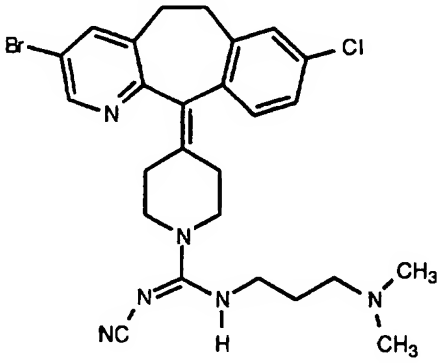
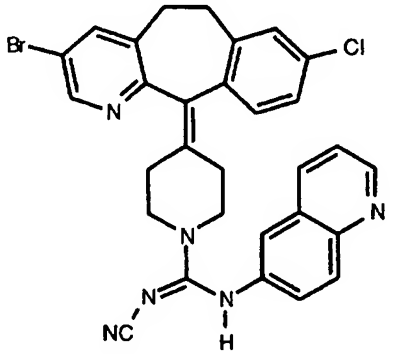
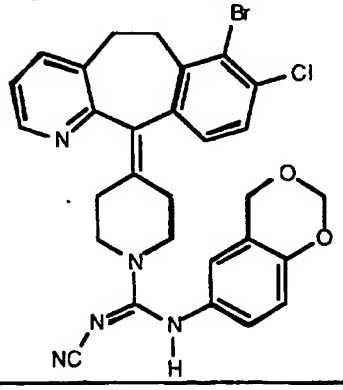
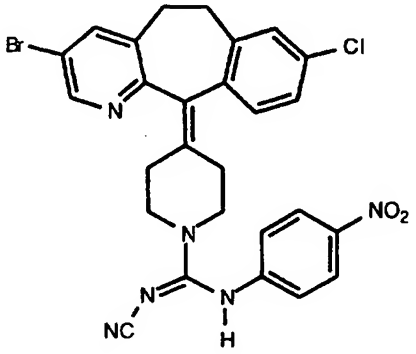
25		0.043	0.27
26		0.029	0.75
27		0.017	2.6
28		0.013	

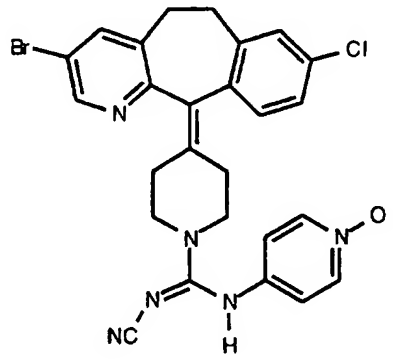
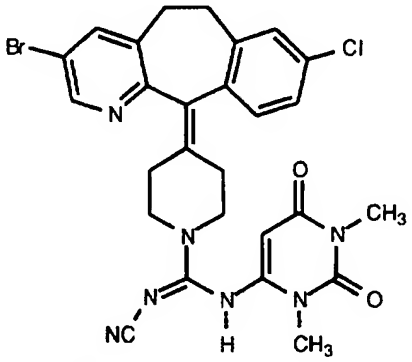
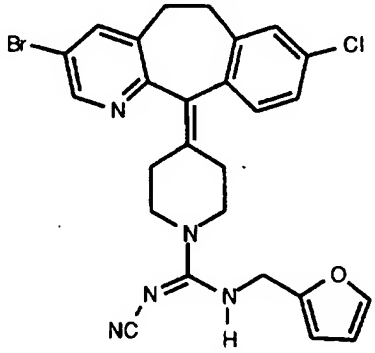
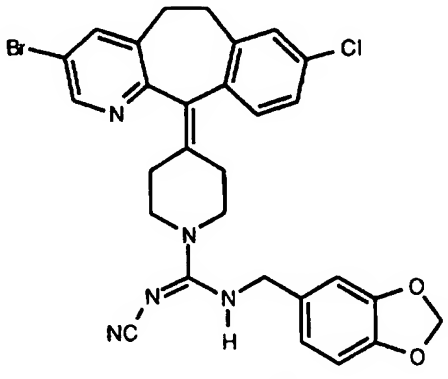
29		0.038	0.57
30		0.155	
31		0.26	
32		0.27	

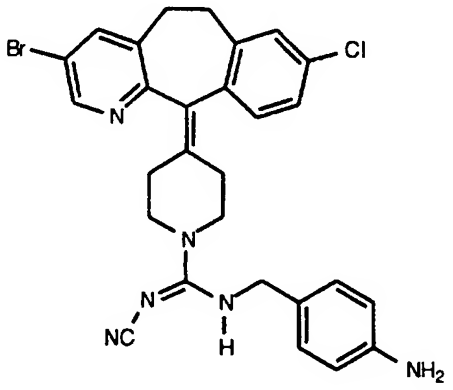
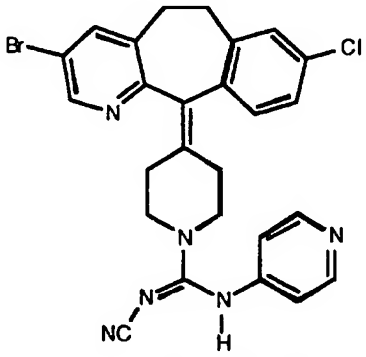
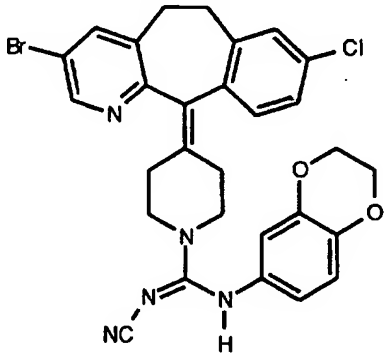
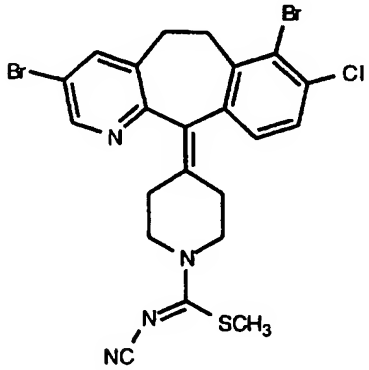
33		2.8	
34		9.6	
35		0.23	
36		0.03	0.28

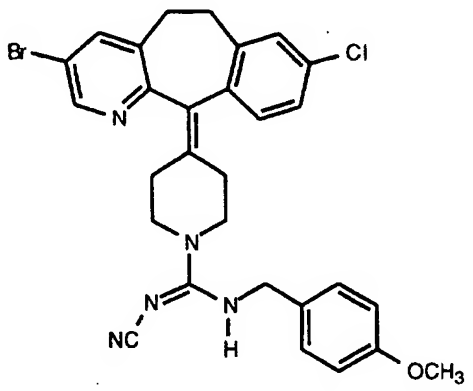
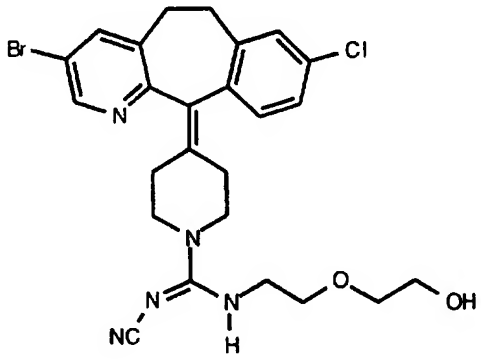
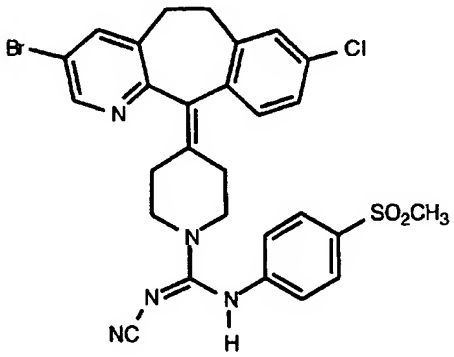
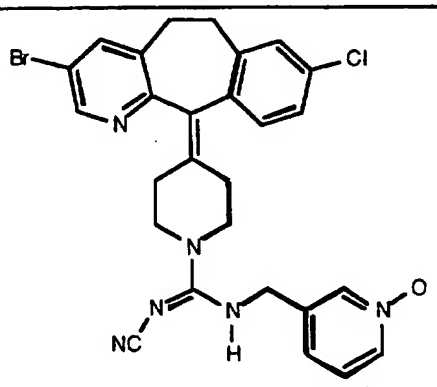
37		0.032	0.28
38		0.32	
39		0.15	
40		0.199	

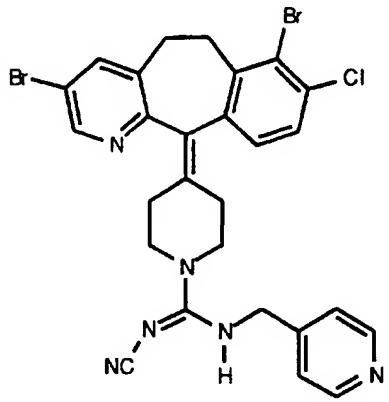
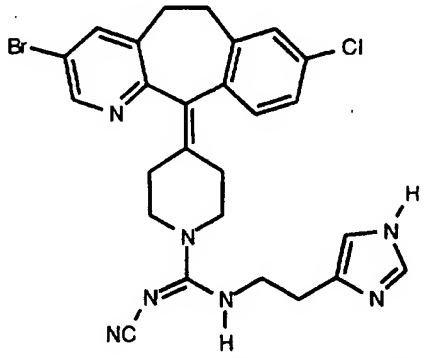
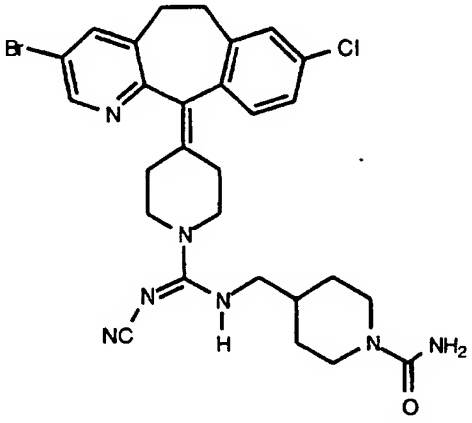
41		0.015	0.7
42		0.035	4.0
43		0.011	
44		0.018	

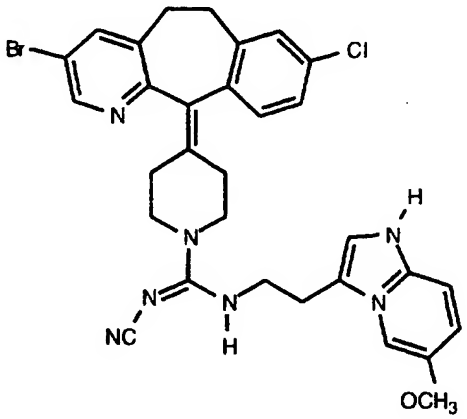
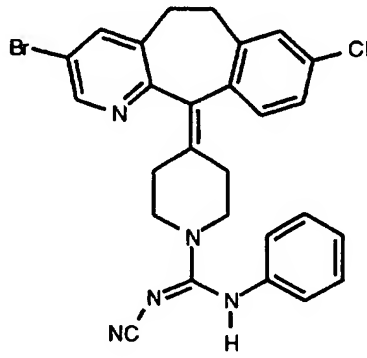
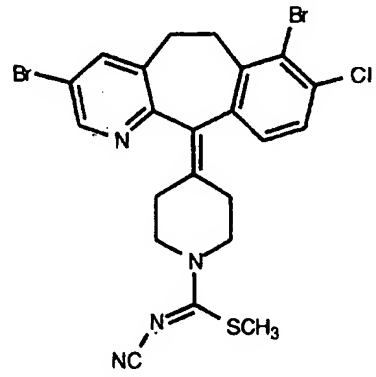
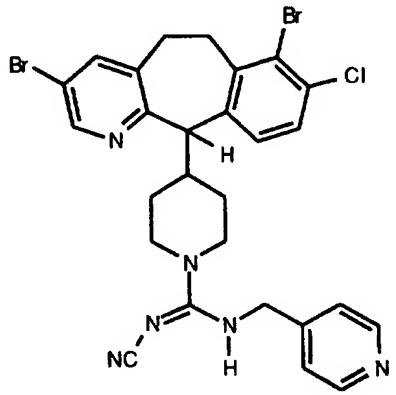
45		0.074	
46		0.15	
47		0.014	
48		0.064	

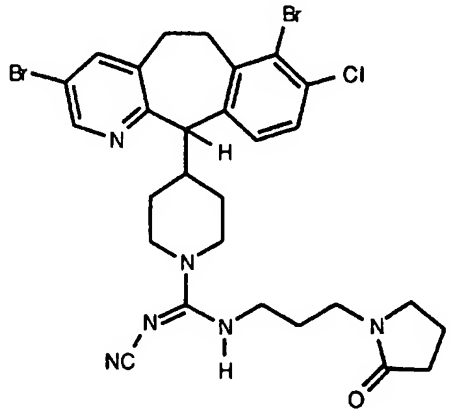
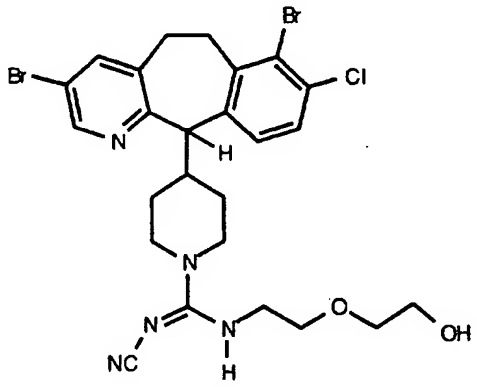
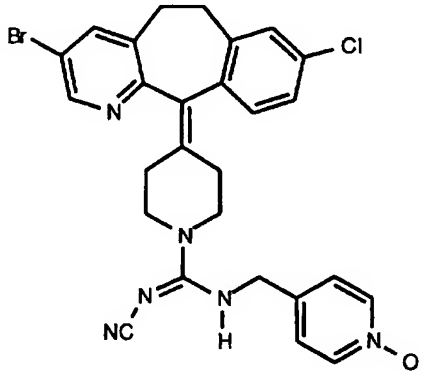
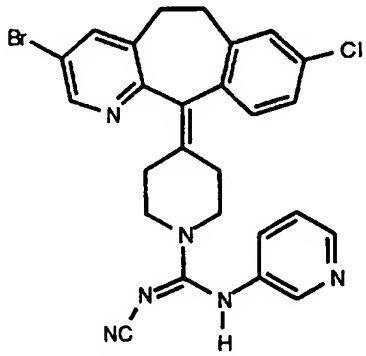
49		0.013	
50		0.3	
51		0.073	
52		0.24	

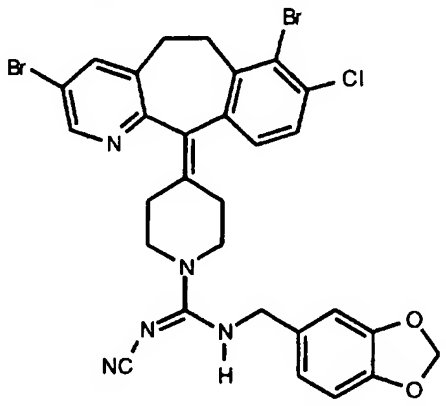
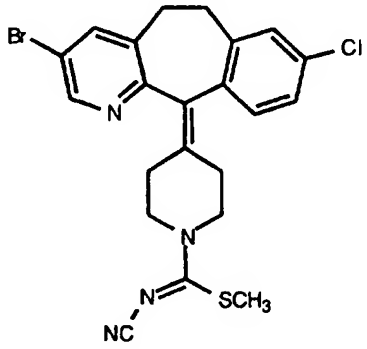
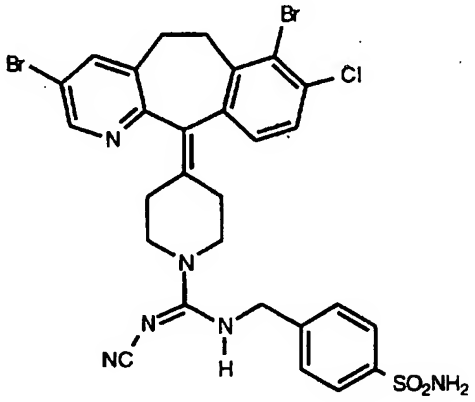
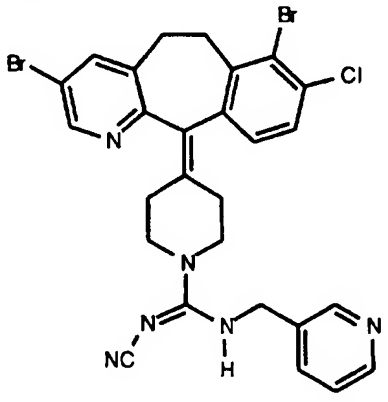
53		0.087	
54		>0.11	
55		0.11	
56		0.042	

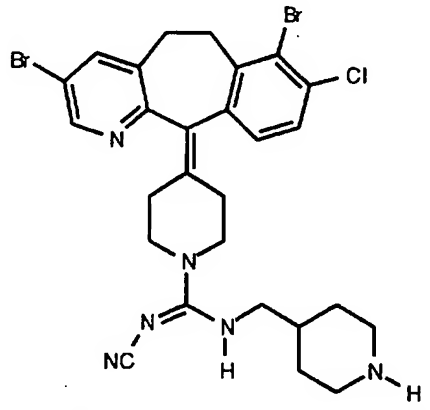
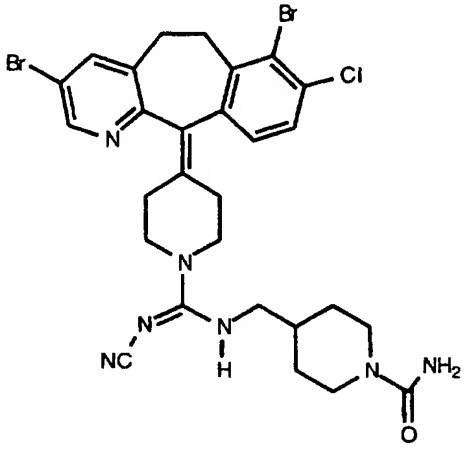
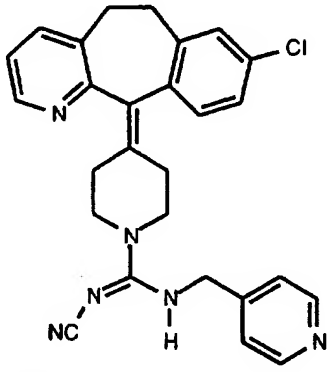
57		0.31	
58		0.084	
59		0.087	
60		0.012	>1.0

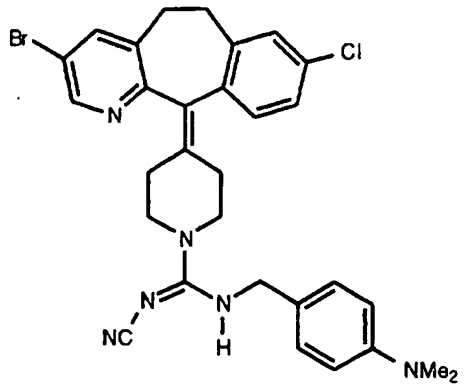
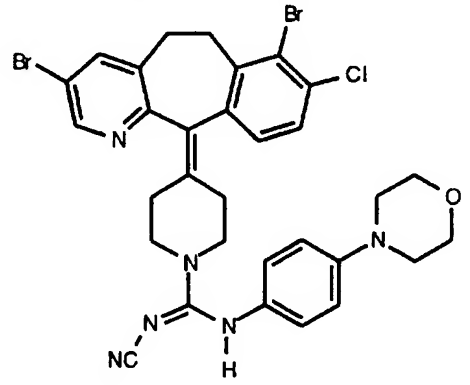
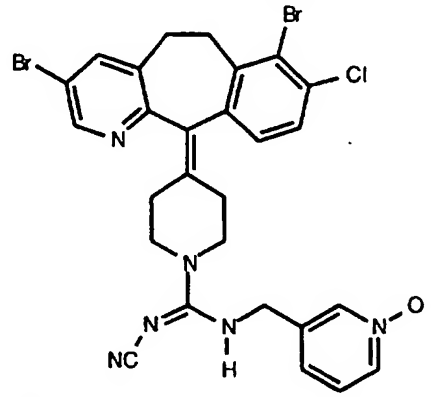
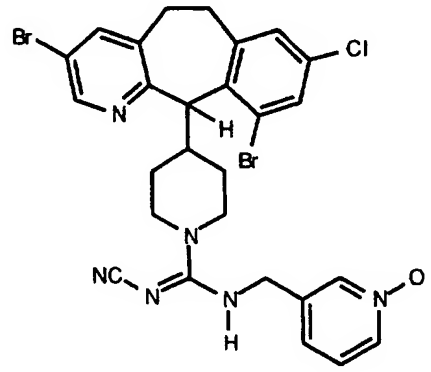
61		0.005	
62		0.058	
63		0.006	

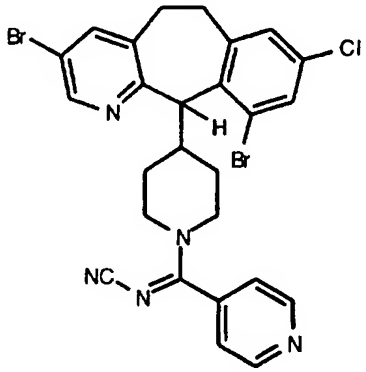
64		>0.95	
65		0.116	
66		0.014	
67		0.0017	

68		0.007	
69		0.0037	
70		0.006	16
71		0.043	

72		>0.10	
73		0.026	
74		0.015	
75		0.0048	

76		0.0047	
77		0.0044	
78		0.064	

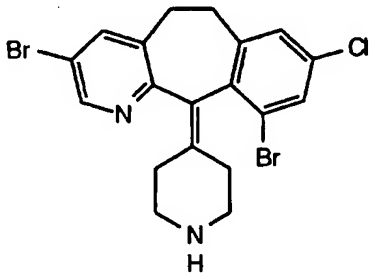
79		0.10	
80		0.038	
81		0.0046	
82		0.0017	

83		>0.033	

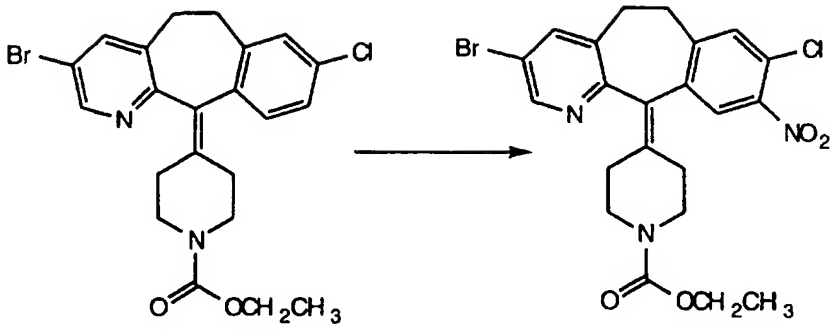
PREPARATION OF STARTING MATERIALS

Starting materials useful in preparing the compounds of the present invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. The tricylic compounds used starting materials, such as compound (2.0), inorganic and organic bases, N-cyanoimidates and alcohols can be prepared using known methods in the art, such as taught in U.S. Patents 5,089,496; 5,151,423; 4,454,143; 4,355,036; PCT /US94/11390 (WO95/10514); PCT/US94/11391 (WO 95/10515); PCT/US94/11392 (WO95/10516); Stanley R. Sandler and Wolf Karo, Organic Functional Group Preparations, 2nd Edition, Academic Press, Inc., San Diego, California, Vol. 1-3, (1983), and in J. March, Advanced Organic Chemistry, Reactions & Mechanisms, and Structure, 3rd Edition, John Wiley & Sons, New York, 1346 pp. (1985). Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

PREPARATIVE EXAMPLE 7

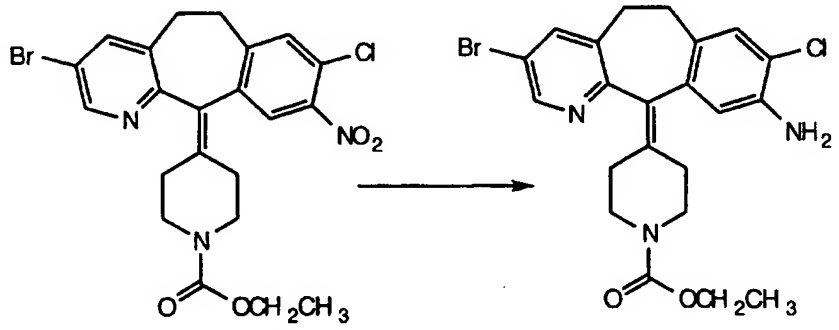


Step A:



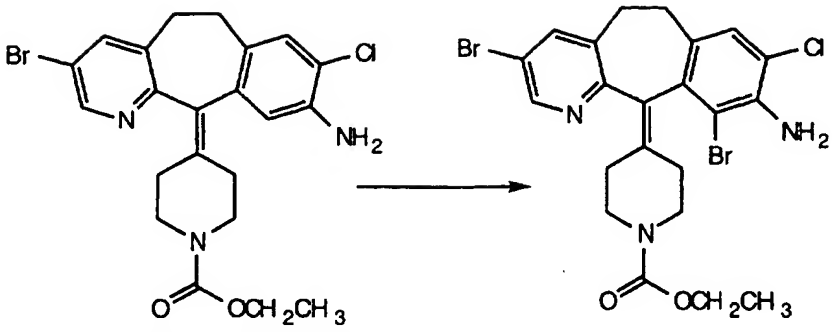
Combine 15 g (38.5 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 150 mL of concentrated H_2SO_4 at -5°C, then add 3.89 g (38.5 mmol) of KNO_3 and stir for 4 hours. Pour the mixture into 3 L of ice and basify with 50% NaOH (aqueous). Extract with CH_2Cl_2, dry over $MgSO_4$, then filter and concentrate *in vacuo* to a residue. Recrystallize the residue from acetone to give 6.69 g of the product.

Step B:



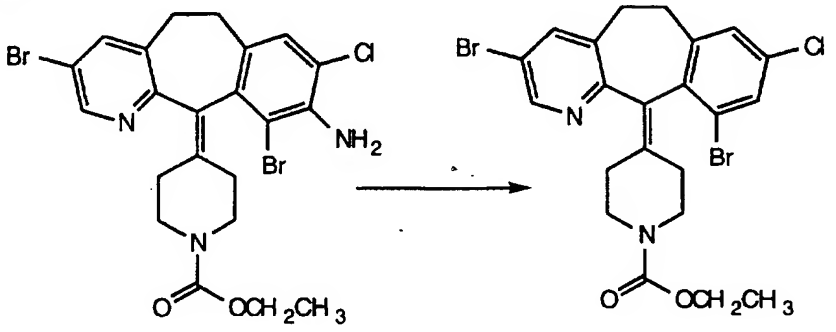
Combine 6.69 g (13.1 mmol) of the product of Step A and 100 mL of 85% EtOH/water, then add 0.66 g (5.9 mmol) of $CaCl_2$ and 6.56 g (117.9 mmol) of Fe and heat the mixture at reflux ovemight. Filter the hot reaction mixture through celite® and rinse the filter cake with hot EtOH. Concentrate the filtrate *in vacuo* to give 7.72 g of the product.

Step C:



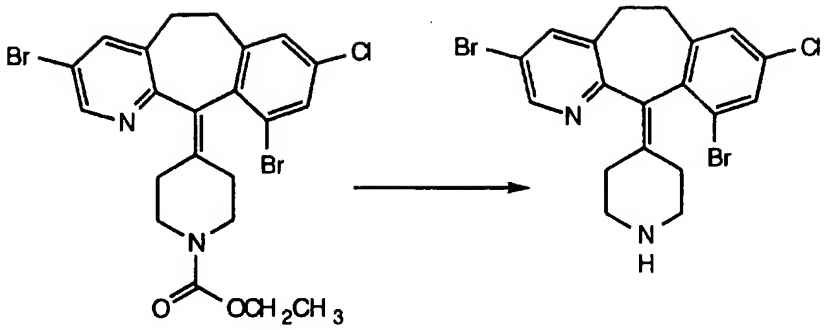
Combine 7.70 g of the product of Step B and 35 mL of HOAc, then add 45 mL of a solution of Br_2 in HOAc and stir the mixture at room temperature overnight. Add 300 mL of 1 N NaOH (aqueous) , then 75 mL of 50% NaOH (aqueous) and extract with EtOAc. Dry the extract over MgSO and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 20%-30% EtOAc/hexane) to give 3.47 g of the product (along with another 1.28 g of partially purified product).

Step D:



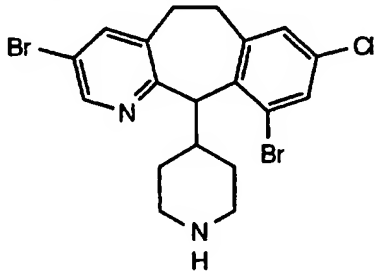
Combine 0.557 g (5.4 mmol) of t-butylnitrite and 3 mL of DMF, and heat the mixtre at to 60°-70°C. Slowly add (dropwise) a mixture of 2.00 g (3.6 mmol) of the product of Step C and 4 mL of DMF, then cool the mixture to room temperature. Add another 0.64 mL of t-butylnitrite at 40°C and reheat the mixture to 60°-70°C for 0.5 hrs. Cool to room temperature and pour the mixture into 150 mL of water. Extract with CH_2Cl_2, dry the extract over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10%-20% EtOAc/hexane) to give 0.74 g of the product.

Step E:



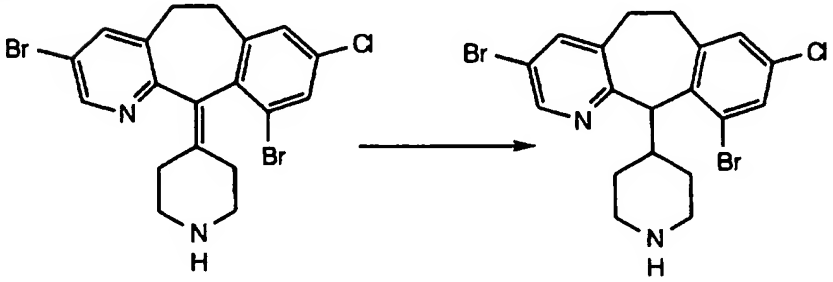
Combine 0.70 g (1.4 mmol) of the product of Step D and 8 mL of concentrated HCl (aqueous) and heat the mixture at reflux overnight. Add 30 mL of 1 N NaOH (aqueous), then 5 mL of 50% NaOH (aqueous) and extract with CH_2Cl_2. Dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 0.59 g of the title compound.

PREPARATIVE EXAMPLE 8



[racemic as well as (+)- and (-)-isomers]

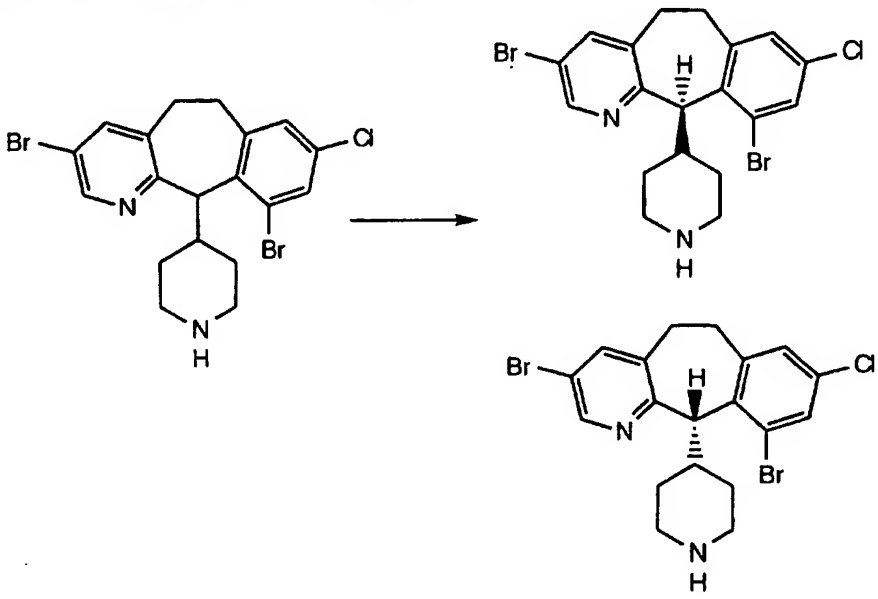
Step A:



Prepare a solution of 8.1 g of the title compound from Preparative Example 7 in toluene and add 17.3 mL of a 1M solution of DIBAL in toluene. Heat the mixture at reflux and slowly add (dropwise) another 21 mL of 1 M DIBAL/toluene solution over a period of 40 min. Cool the reaction mixture to about 0°C and add 700 mL of 1 M HCl (aqueous). Separate and discard the organic phase. Wash the aqueous phase with CH_2Cl_2, discard the extract, then basify the aqueous phase by adding

50% NaOH (aqueous). Extract with CH_2Cl_2, dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 7.30 g of the title compound, which is a racemic mixture of enantiomers.

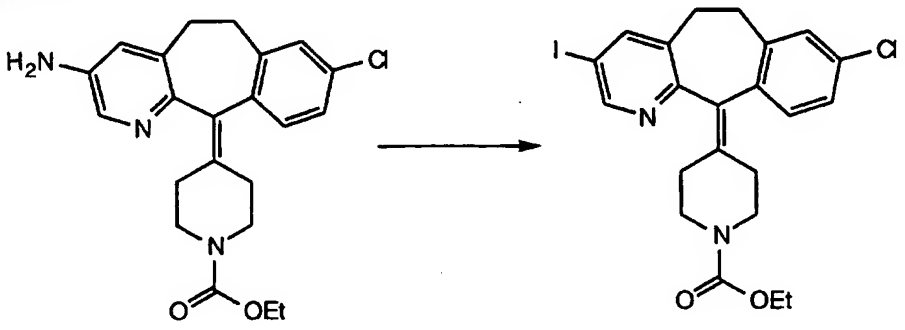
Step B - Separation of Enantiomers:



The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 20% iPrOH/hexane + 0.2% diethylamine), to give the (+)-isomer and the (-)-isomer of the title compound.

PREPARATIVE EXAMPLE 48

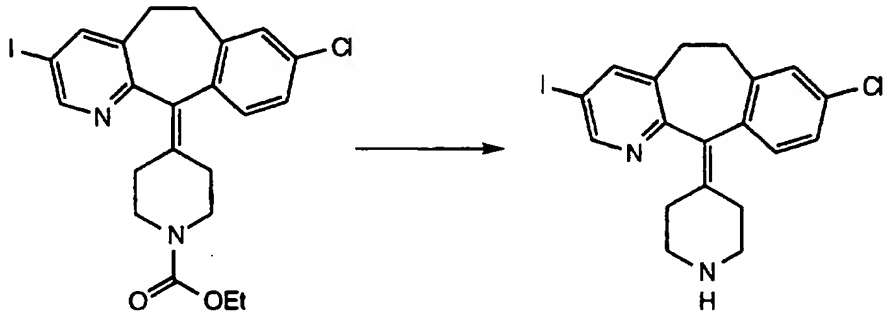
Step A:



Combine 6 g (15.11 mmol) of the title compound of WO 95/10516's Preparative Example 47B, and benzene, and add 2.3 g (9.06 mmol) of iodine. Heat the mixture at reflux for 3 hours, cool, then dilute with 50 mL

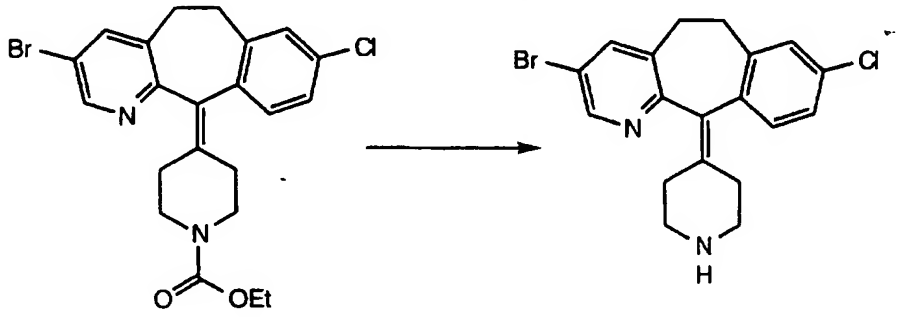
of CH_2Cl_2. Wash the organic phase with 5% $NaHSO_3$(aqeuous) (3 x 80 mL), then with 1M NaOH (aqueous) (2x 80 mL), and dry over $MgSO_4$. Concentrate to a residue chromatograph (silica gel, 30% EtOAc/hexanes), to give 3.2 g (42% yield) of the product iodo compound. Mass Spec.: MH+ = 509

Step B:



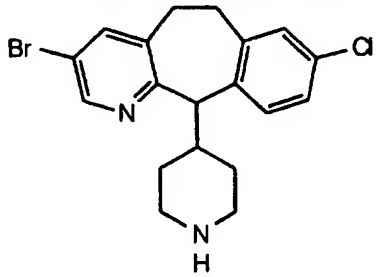
The product of Step A is hydrolyzed via substantially the same procedure as described in Example 358, Step A, of WO 95/10516, to give the iodoamine product in 89% yield.

PREPARATIVE EXAMPLE 49

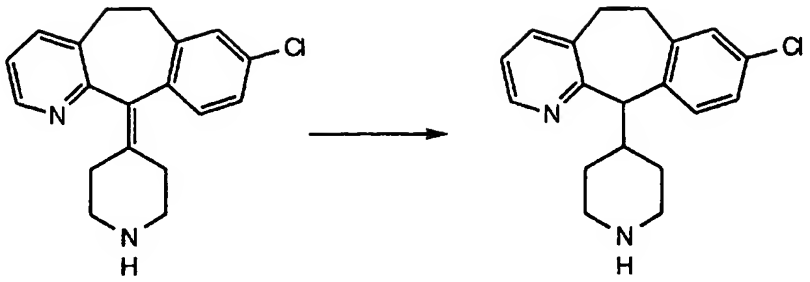


The product of Preparative Example 47, Step C, of WO 95/10516, (2.42 g) is hydrolyzed via substantially the same procedure as described in Example 358, Step A, of WO 95/10516, to give 1.39 g (69% yield) of the bromoamine product.

PREPARATIVE EXAMPLE 51A

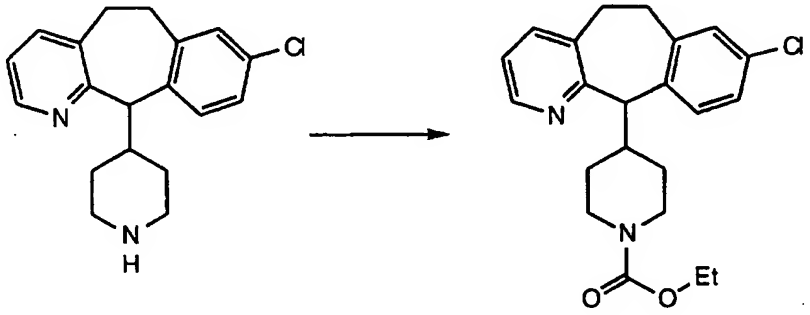


Step A:



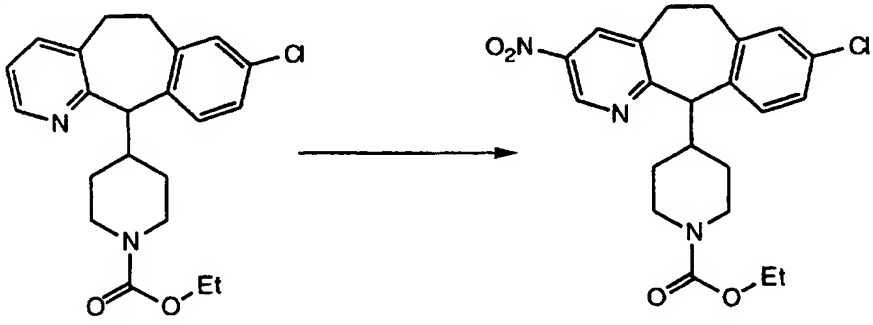
Combine 82.0 g (0.26 mole) of the product of Preparative Example 1, Step G, of WO 95/10516, and 1 L of toluene, then add 20.06 g (0.53 mole) of $LiAlH_4$ and heat the reaction mixture at reflux overnight. Cool the mixture to room temperature and add ~1 L of Et_2O, followed by dropwise addition of saturated Na_2SO_4 (aqueous) until a precipitate forms. Filter and stir the filtrate over $MgSO_4$ for 30 minutes, then concentrate *in vacuo* to give the product compound in 83% yield. Mass Spec.: $MH^+ = 313$

Step B:



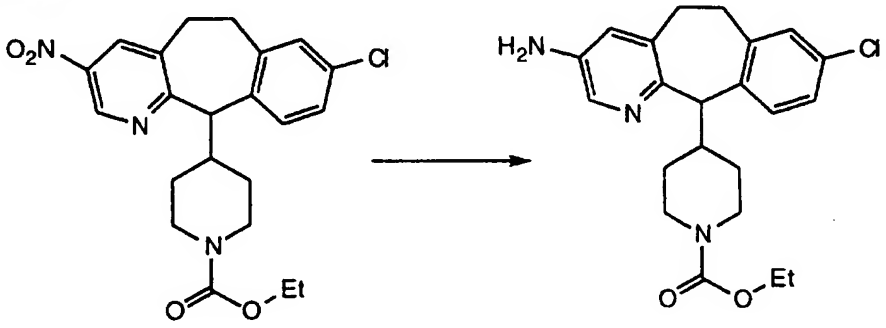
Combine 24.32 g (74.9 mmol) of the Product from Step A, 500 mL of toluene, 83 mL of Et_3N and 65.9 mL of ethyl chloroformate and heat the mixture at reflux overnight. Cool to 25°C, pour into 200 mL of water and extract with EtOAc. Dry the extract over $MgSO_4$, concentrate *in vacuo* to a residue and chromatograph (silica gel, 50% EtOAc/hexane) to give 15 g of the product compound. Mass Spec.: $MH^+ = 385$.

Step C:



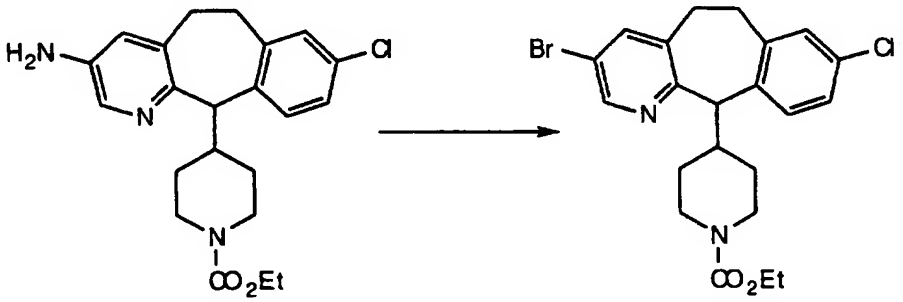
Dissolve 3.2 g (10.51 mmol) of tetra-n-butylammonium nitrate in 25 mL of CH_2Cl_2 and add 2.2 g (10.51 mmol, 1.5 mL) of TFAA. Cool to 0°C and add the mixture (via cannula) to a solution of 3.68 g (9.56 mmol) of the product of Step B in 50 mL of CH_2Cl_2 at 0°C, then stir at 0°C for 3 hours. Allow the mixture to warm to 25°C while stirring overnight, then extract with saturated $NaHCO_3$ (aqueous) and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 30% EtOAc/hexane) to give 1.2 g of the product compound. Mass Spec.: $MH^+ = 430$

Step D:



Combine 2.0 g (4.7 mmol) of the Product of Step C and 150 mL of 85% EtOH (aqueous), add 2.4 g (42 mmol) of Fe filings and 0.24 g (2.1 mmol) of $CaCl_2$, and heat at reflux for 16 hours. Filter the hot mixture through a bed of celite®, wash the celite® with hot EtOH. Concentrate the filtrate *in vacuo* to give a 100% yield of the product compound. Mass Spec.: $MH^+ = 400$.

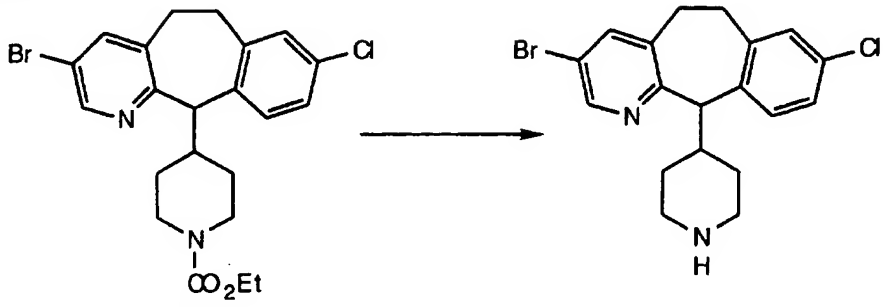
Step E:



Combine 2.0 g (5.2 mmol) of the Product of Step D and 20 mL of 48% HBr, cool the mixture to -5°C. Stir the mixture at -5°C for 15 minutes and slowly add a solution of 1.07 g (15.5 mmol) of $NaNO_2$ in 10 mL of water. Stir for 45 minutes, then quench with 50% NaOH (aqueous) to pH ~10. Extract with EtOAc, dry the combined extracts over $MgSO_4$ and

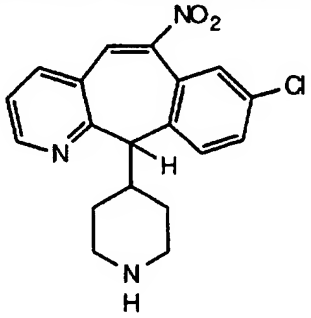
concentrate *in vacuo* to give the product compound. Mass Spec.: MH^+= 465

Step F:

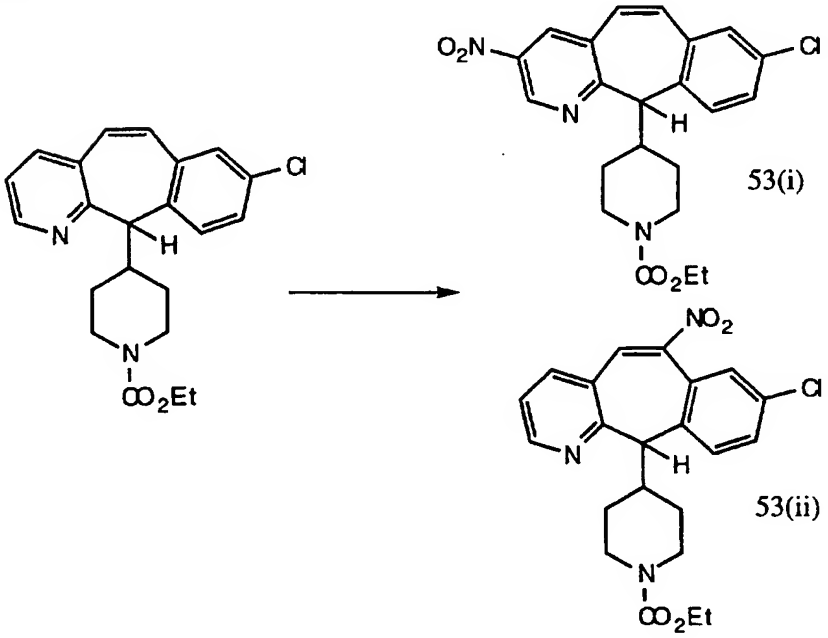


Hydroyze 4.0 g of the Product of Step E via substantially the same process as described for Example 358, Step A, of WO 95/10516, to give 1.39 g of the product compound. Mass Spec.: MH^+ = 392

PREPARATIVE EXAMPLE 53



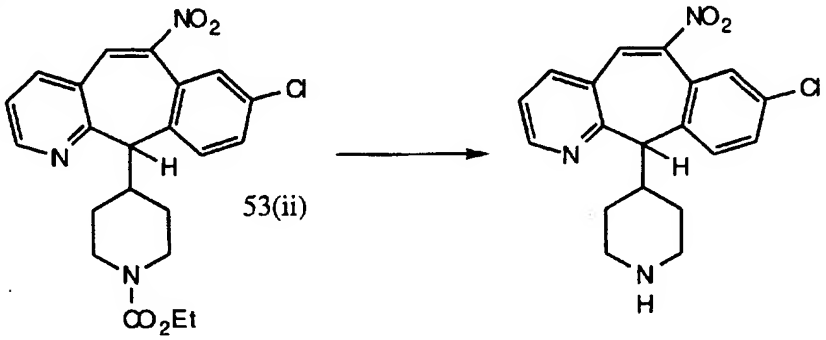
Step A:



Combine 14.95 g (39 mmol) of the Product of Preparative Example 34A, of WO 95/10516, and 150 mL of CH_2Cl_2, then add 13.07 g (42.9 mmol) of $(nBu)_4NNO_3$ and cool the mixture to 0°C. Slowly add (dropwise) a solution of 6.09 mL (42.9 mmol) of TFAA in 20 mL of CH_2Cl_2 over 1.5 hours. Keep the mixture at 0°C overnight, then wash successively with saturated $NaHCO_3$ (aqueous), water and brine. Dry the organic solution over Na_2SO_4, concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, EtOAc/hexane gradient) to give 4.32 g and 1.90 g of the two product compounds 53(i) and 53(ii), respectively.

Mass Spec.(53(i)): MH^+ = 428.2; Mass Spec. (53(ii)): MH^+ = 428.3

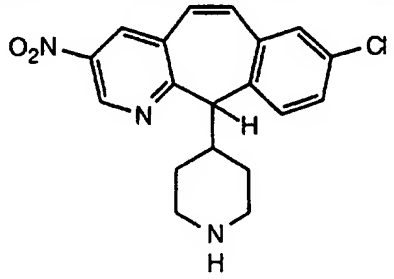
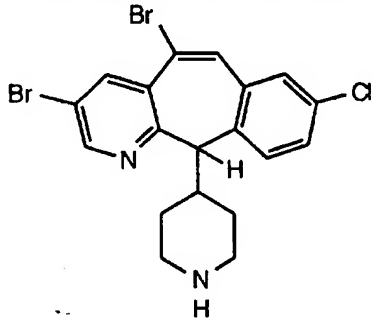
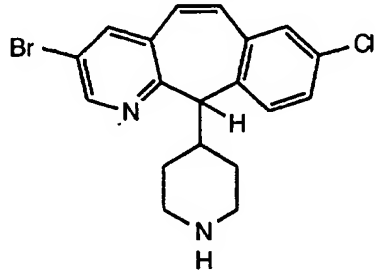
Step B:



The compound 53(ii) from Step A (0.20 g) is hydrolyzed via substantially the same procedure as described for Example 358, Step A, of WO 95/10516 (published April 20, 1995), to give 0.16 g of the product compound.

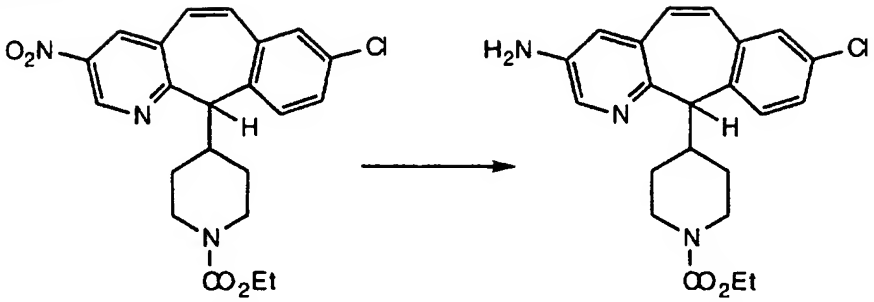
Using the starting compound indicated and substantially the same procedure as described in Preparative Example 53, Step B, the compounds in Table 1 are prepared:

TABLE 1

Starting Compound	Compound	Analytical Data
Preparative Example 53, Step A, compound 53(i)	 Preparative Example 53A	---
Preparative Example 54, Step B, compound 54(ii)	 Preparative Example 53B	Mass Spec.: MH^+ = 466.9
Preparative Example 54, Step B, compound 54(i)	 Preparative Example 53C	Mass Spec.: MH^+ = 466.9

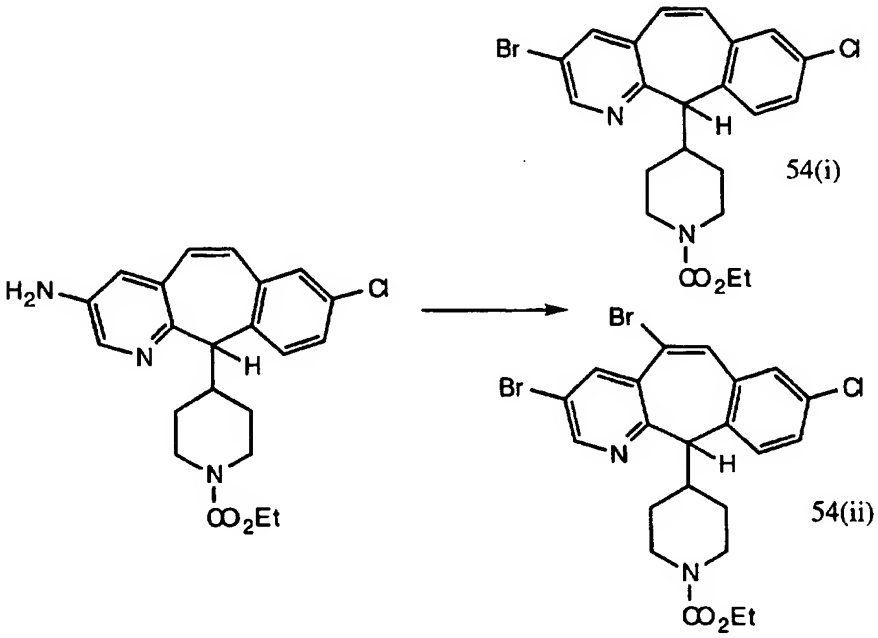
PREPARATIVE EXAMPLE 54

Step A:



Combine 22.0 g (51.4 mmol) of the product 53(i) from Preparation 53, Step A, 150 mL of 85% EtOH (aqueous), 25.85 g (0.463 mole) of Fe powder and 2.42 g (21.8 mmol) of $CaCl_2$, and heat at reflux overnight. Add 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of $CaCl_2$ and heat at reflux for 2 hours. Add another 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of $CaCl_2$ and heat at reflux for 2 hours more. Filter the hot mixture through celite®, wash the celite® with 50 mL of hot EtOH and concentrate the filtrate *in vacuo* to a residue. Add 100 mL of anhydrous EtOH, concentrate to a residue and chromatograph the residue (silica gel, MeOH/CH_2Cl_2 gradient) to give 16.47 g of the product compound.

Step B:



54(i)

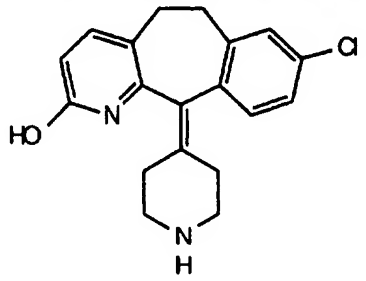
54(ii)

Combine16.47 g (41.4 mmol) of the product compound from Preparative Example 54, Step A, and 150 mL of 48% HBr (aqueous) and

cool to -3°C. Slowly add (dropwise) 18 mL of bromine, then slowly add (dropwise) a solution of 8.55 g (0.124 mole) of $NaNO_2$ in 85 mL of water. Stir for 45 minutes at -3° to 0°C, then adjust to pH = 10 by adding 50% NaOH (aqueous). Extract with EtOAc, wash the extracts with brine and dry the extracts over Na_2SO_4. Concentrate to a residue and chromatograph (silica gel, EtOAc/hexane gradient) to give 10.6 g and 3.28 g of the two product compounds 54(i) and 54(ii), respectively.

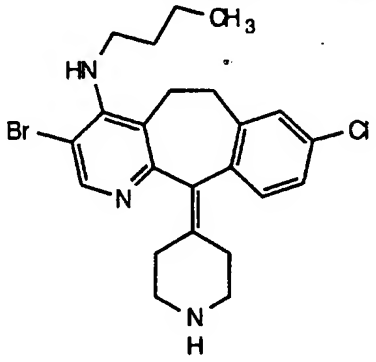
Mass Spec. (54(i)): MH^+ = 461.2; Mass Spec. (54(ii)): MH^+ = 539

PREPARATIVE EXAMPLE 55

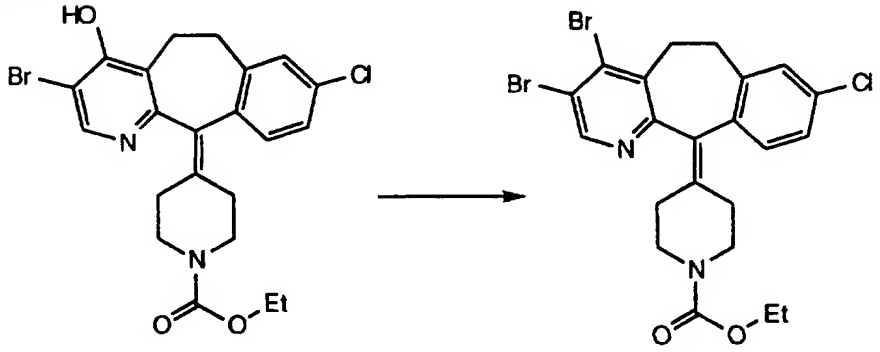


The title compound is known and is prepared by the procedure described in Bioorg. & Med. Chem. Lett., 3, (No. 6) 1073-1078 (1993).

PREPARATIVE EXAMPLE 56

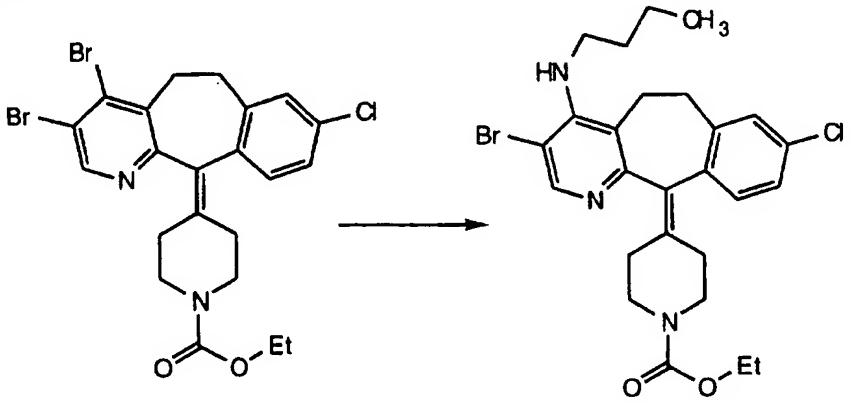


Step A:



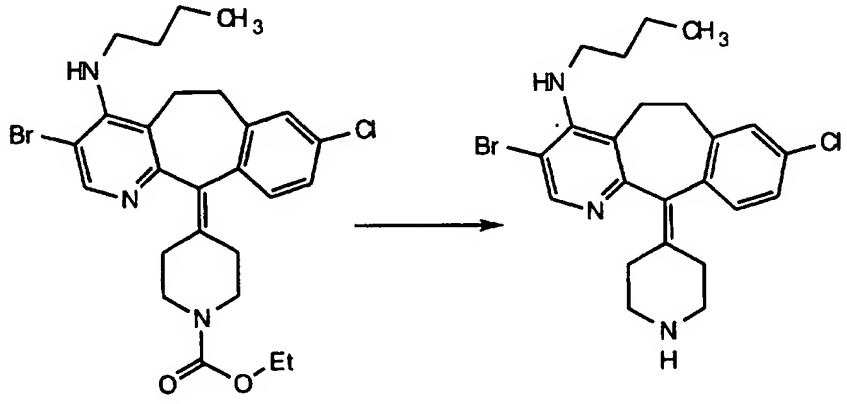
Combine 2.04 g of the product of Preparative Example 44, of WO 95/10516 (published April 20, 1995), 1.3 mL of PBr_3, 1.0 mL of Et_3N and 20 mL of CH_2Br_2, and heat the mixture at reflux overnight. Cool the mixture, dilute with CH_2Cl_2 and wash with 1 N NaOH (aqueous). Dry over $MgSO_4$ and concentrate *in vacuo* to give 1.22 g (53% yield) of the product compound. Mass Spec.: $MH^+ = 541$

Step B:



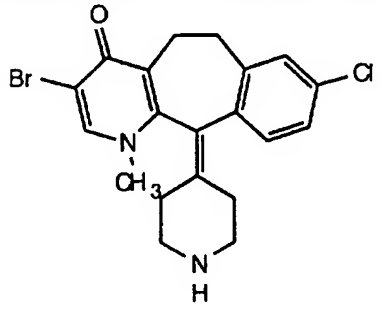
Combine 0.3 g of the product compound from Preparative Example 56, Step A, and 8 mL of n-butylamine and stir at 120°C in a sealed tube for 48 hours. Concentrate *in vacuo* to a residue and purify by preparative plate chromatography (silica gel, 1.5-2.5% $MeOH/CH_2Cl_2$) to give 80 mg (27%) yield of the product compound. Mass Spec.: $MH^+ = 534$

Step C:

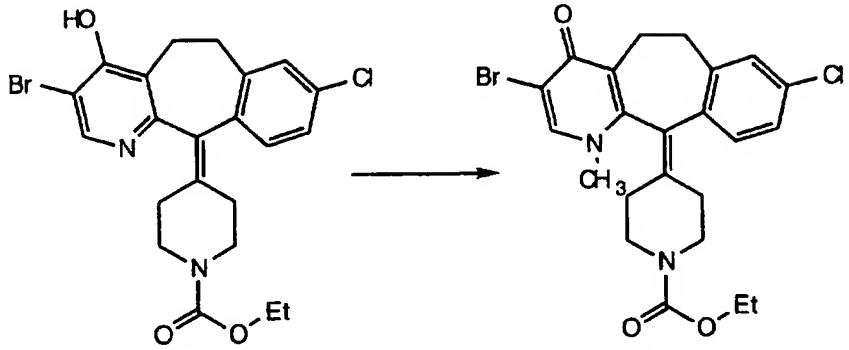


Combine 66 mg of the product compound from Preparative Example 56, Step B, 4 mL of anhydrous EtOH, and 15 mL of concentrated HCl stir at reflux for 60 hours. Cool the reaction mixture to about 0°C and basify by adding KOH. Extract with CH_2Cl_2, dry the extract over $MgSO_4$, and concentrate *in vacuo* to give 46 mg (81% yield) of the product compound. Mass Spec.: $MH^+ = 462$

PREPARATIVE EXAMPLE 57

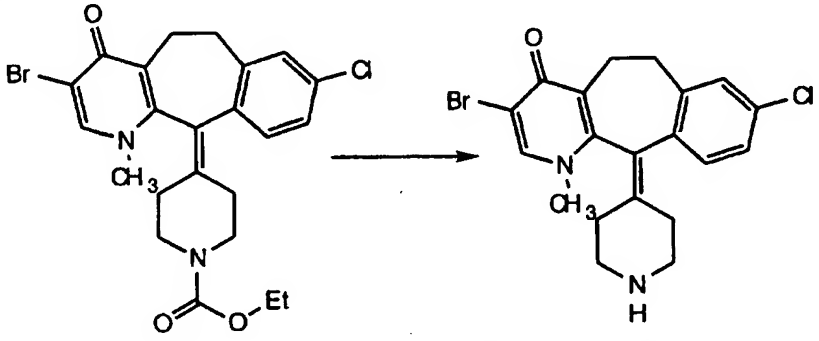


Step A:



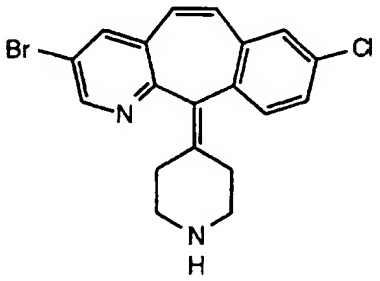
Combine 1.19 g of the product of Preparative Example 44, of WO 95/10516, 10 mL of anhydrous DMF, 0.2 g of NaH (60% in mineral oil) and 0.19 mL of methyl iodide, and stir at room temperature overnight. Concentrate *in vacuo* to a residue, dilute the residue with CH_2Cl_2, wash with saturated $NaHCO_3$ (aqueous), and dry over $MgSO_4$. Concentrate *in vacuo* to give 1.13 g (92% yield) of the product compound. Mass Spec.: $MH^+ = 493$.

Step B:

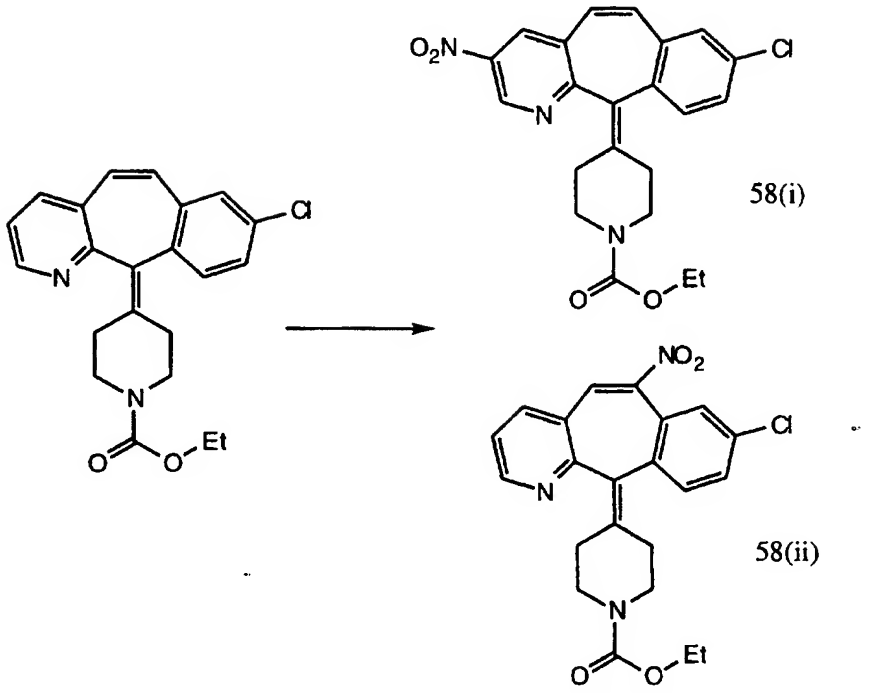


Hydrolyze 1.13 g of the product of Step A via substantially the same procedure as described for Preparative Example 56, Step C, to give 0.61 g (63% yield) of the product compound.

PREPARATIVE EXAMPLE 58

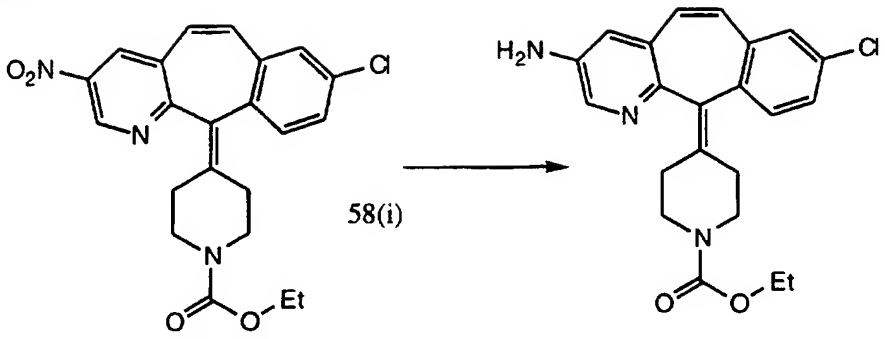


Step A:



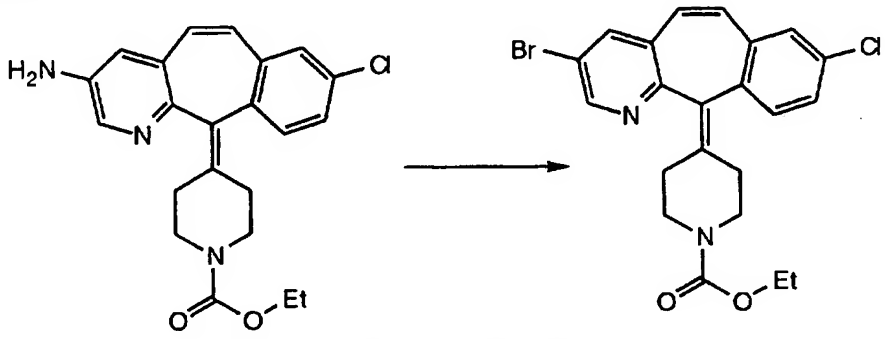
Combine 1.07 g (3.52 mmol) of tetrabutylammonium nitrate, 4 mL of anhydrous CH_2Cl_2 and 0.743 g (3.52 mmol) of TFAA, and add the resulting mixture to a solution of 1.22 g (3.20 mmol) of the title compound of Preparative Example 37, of WO 95/10516, in 8 mL of anhydrous CH_2Cl_2 at room temperature. Stir at room temperature overnight, then wash with 20 mL of saturated $NaHCO_3$ (aqueous) and 20 mL of brine, and dry over $MgSO_4$. Concentrate *in vacuo* and chromatograph the resulting residue (silica gel, EtOAc/hexane) to give 0.216 g of the product compound 58(i) and 0.27 g of the product compound 58(ii). Mass Spec. (58(i)): MH^+ =426. m.p. (58(i)) 97.5° - 99.2°C.

Step B:



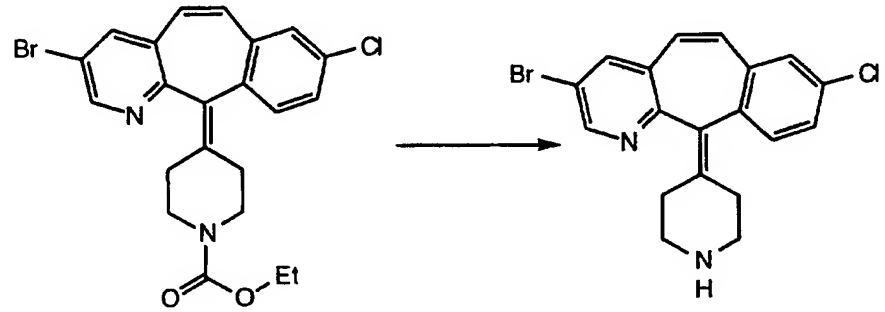
Reduce the product 58(i) from Step A via essentially the same procedure as described in Preparative Example 47, Step B, of WO 95/10516, to give the product compound. Mass Spec.: MH^+ = 396

Step C:



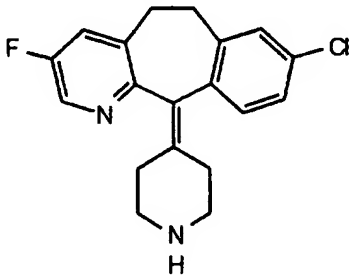
React the product from Step B with HBr and bromine via essentially the same procedure as described in Preparative Example 47, Step C, of WO 95/10516, to give the product compound. Mass Spec.: MH^+ = 459

Step D:

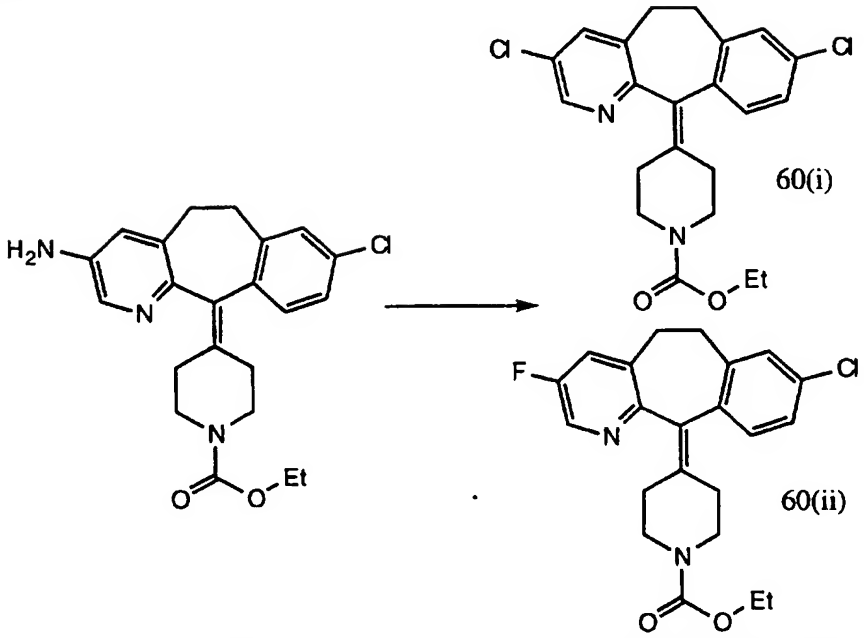


Hydrolyze 0.83 g of the product from Step C via essentially the same procedure as described in Preparative Example 56, Step C, to give 0.56 g of the product compound. Mass Spec.: MH^+ = 387

PREPARATIVE EXAMPLE 60

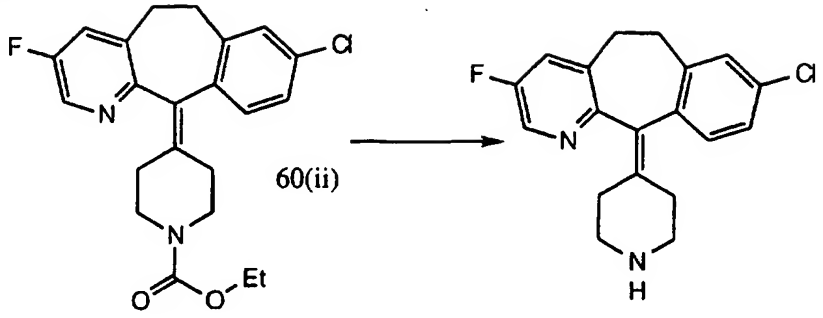


Step A:



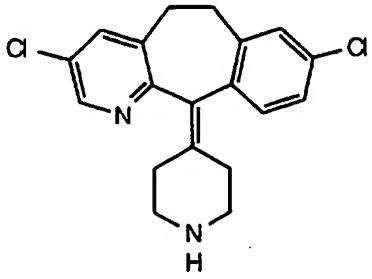
Combine 16.25 g (40.83 mmol) of the product of Preparative Example 47, Step B, of WO 95/10516, and a slurry of 7.14 g (61.11 mmol) of $NOBF_4$ in 100 mL of CH_2Cl_2 and stir the mixture for 3 hours. Add 100 mL of o-dichlorobenzene and heat for 5 hours, distilling the CH_2Cl_2 from the mixture. Concentrate *in vacuo* to a residue, add 200 mL of CH_2Cl_2 and wash with water (2 X 200 mL). Dry over $MgSO_4$, concentrate *in vacuo* to a residue, and chromatograph (silica gel, 20% EtOAc/hexane) to give 4.1 g of product compound 60(i) and 4.01 g of Product compound 60(ii). Mass Spec. (60 (i)): MH^+ = 418. Mass Spec. (60 (ii)): MH^+ = 401

Step B:



Hydrolyze 3.4 g of the product 60 (ii) from Step A via essentially the same process as described for Example 358, Step A, of WO 95/10516, to give 3.01 g of product compound. Mass Spec.: MH^+ = 329

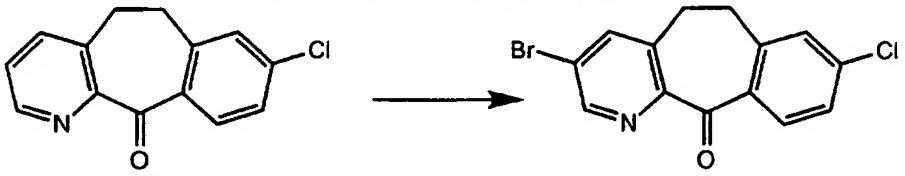
Using compound 60(i) from Preparative Example 60, Step A, and following substantially the same procedure as described in Preparative Example 60, Step B, the compound:



(Preparative Example 60A)

was prepared. Mass Spec.: MH^+ = 346.

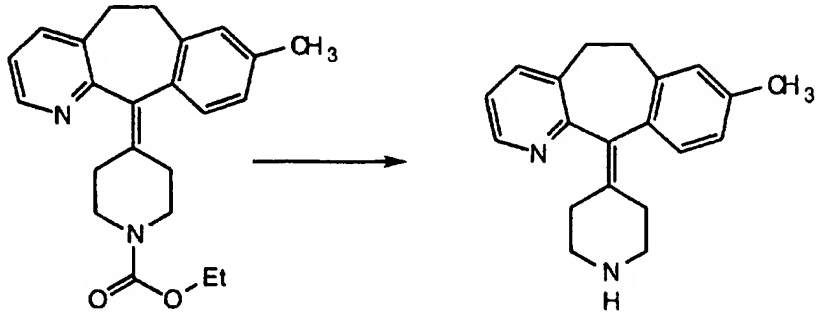
PREPARATIVE EXAMPLE 66



Cool 50.0 g (20.5 mmol) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one to 0°C, slowly add 75 mL (93.69 mmol) of sulfur monochloride over 20 minutes, then slowly add 25 mL (48.59 mmol) of Br_2 over 15. Heat at 95°C for 20 hour, add 12.5 mL (24.3 mmol) of Br_2 and heat for a another 24 hours. Cool the mixture, and slowly add to a mixture of CH_2Cl_2 and 1N NaOH (aqueous) at 0°C. Wash the organic phase with water, dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 500 mL CH_2Cl_2 then 0.2%-5% (10% NH_4OH in MeOH)/CH_2Cl_2), then chromatograph again

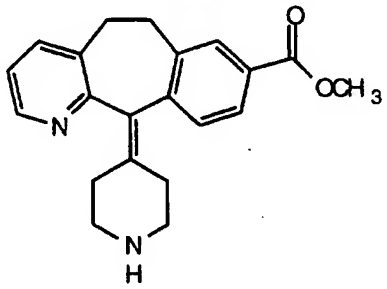
(silica gel, 3%-8.5% EtOAc/hexane) to give 8.66 g of the product compound. Mass Spec.: $MH^+ = 322$

PREPARATIVE EXAMPLE 67

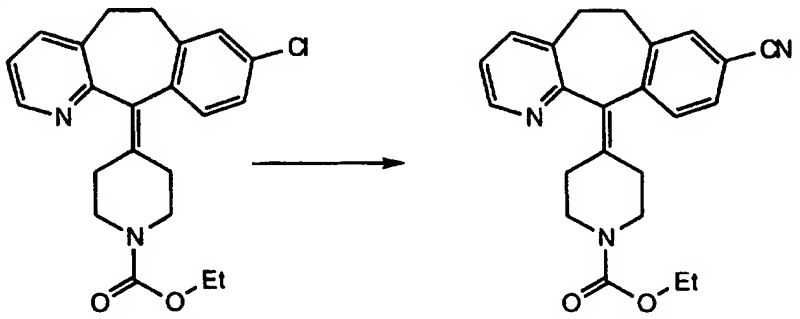


Dissolve 0.16 g (0.46 mmol) of 4-(8-methyl-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidine)-1-ethoxycarbonyl-piperidine, in 2 mL EtOH and add 4 mL of 12 N HCl. Heat the solution for 3 hours at 85°C, then cool to 25°C. Adjust to pH = 10 with 50% NaOH (aqueous) and extract several times with 50 mL of EtOAc. Combine the organic layers, dry them over $MgSO_4$, and concentrate *in vacuo* to give the product compound.

PREPARATIVE EXAMPLE 68



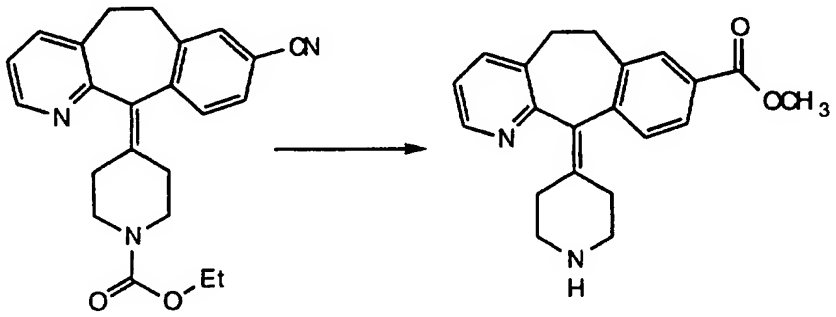
Step A:



Disolve 2 g (5.22 mmol) of the title compound of Preparative Example 1F, of WO 95/10516, in 2.6 mL of dry N-methylpyrrolidinone. Add 0.87 g (9.4 mmol) of CuCN and 0.139 g (0.93 mmol) of sodium iodide. Heat the mixture at 200°C under nitrogen for 20 hours, cool to 25°C and

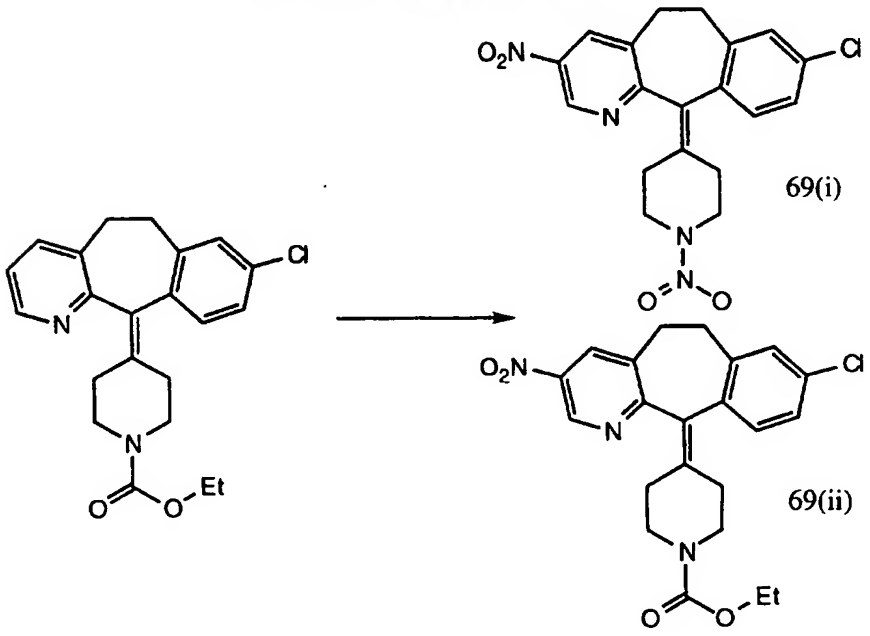
repeatedly grind and mix with five 50 mL portions of CH_2Cl_2 and 7 M NH_4OH (aqueous). Wash the organic layer with 7 M NH_4OH until the organic layer is no longer blue or green. Dry the combined organic layers over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph (silica gel 70% EtOAc/hexane), then recrystallize from EtOAc/hexane to give the product compound. m.p. = 152.4°-153.5°C; Mass Spec.: MH^+ = 374

Step B:



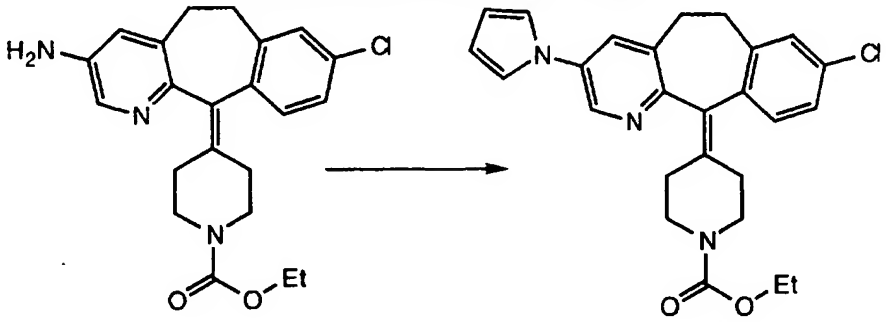
Dissolve 4.08 g (10.93 mmol) of the product of Step A in 12 M HCl and heat at 85°C for 18 hours. Concentrate *in vacuo* to a residue. Dissolve the residue in 175 mL of MeOH, saturate with HCl gas, and heat at reflux for 18 hours. Concentrate *in vacuo* to give the product compound as its HCl salt. Mass Spec.: MH^+ = 335

PREPARATIVE EXAMPLE 69



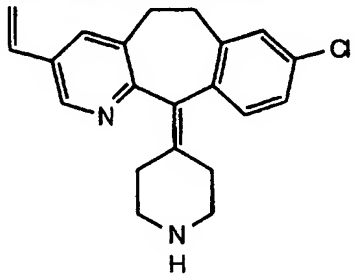
Combine 75 g (0.196 mole) of the Product of Example 1, Step F, of WO 95/10516, and 300 mL of CH_2Cl_2 at 0°C, and slowly add (dropwise) a solution of 72 g (0.236 mole) of tetrabutylammonium nitrate and 35 mL (0.247 mole) of TFAA in 500 mL of CH_2Cl_2. Stir at 25°C overnight, slowly add (dropwise) 1 L of saturated $NaHCO_3$ (aqueous). Separate the layers, wash the organic phase with brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue, chromatograph twice (1 kg silica gel, gradient of EtOAc/CH_2Cl_2) to give 8.63 g of product compound 69(i), and 34 g of product compound (ii). Recrystallize compound 69(i) from CH_2Cl_2/hexane to give the purified product compound 69(i). m.p.= 186°-187°C; Mass Spec.: (FAB) MH^+ = 401

PREPARATIVE EXAMPLE 69A

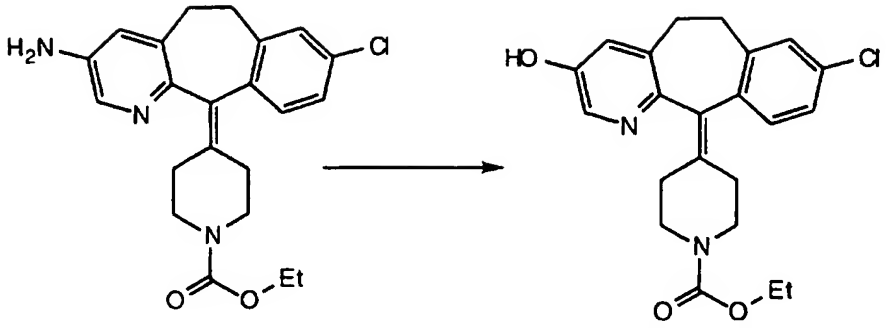


Combine 0.4 g (1 mmol) of the Product of Example 47, Step B, of WO 95/10516 (published April 20, 1995), and 0.2 mL (1.2 mmoles) of 2, 5-diethoxytetrahydrofuran in 3 mL of glacial HOAc, and heat at reflux for 1.5 hours. Cool the mixture, wash with saturated $NaHCO_3$ (aqueous), then with brine, dry over $MgSO_4$, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 5%-15% EtOAc/CH_2Cl_2) to give 0.34 g of the product compound. Mass Spec.: (FAB) MH^+ = 448

PREPARATIVE EXAMPLE 70

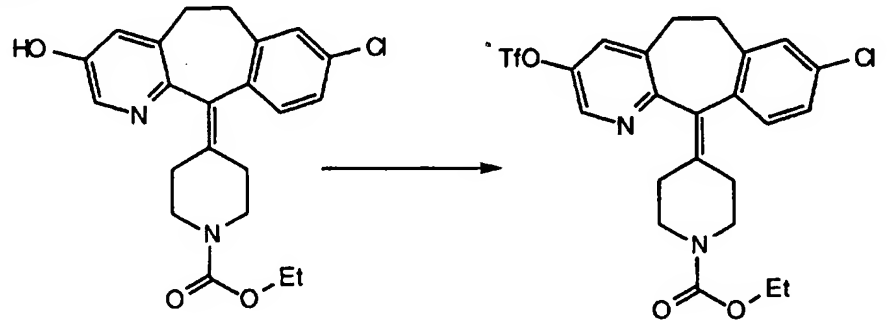


Step A:



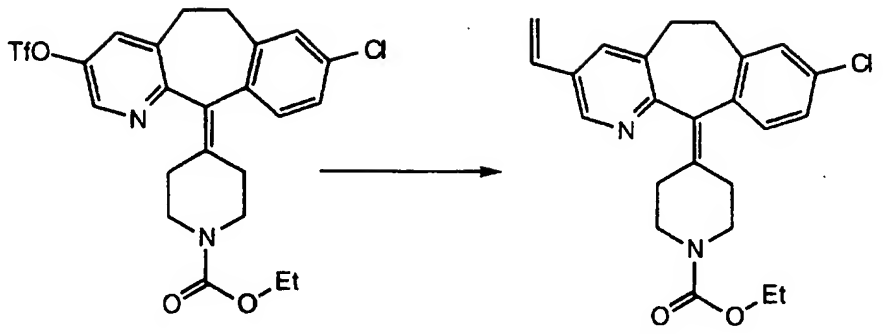
Combine 13.8 g (34.7 mmol) of the Product of Example 47, Step B, of WO 95/10516, and 90 mL of water at 0°C, add a solution of 6.9 mL of concentrated H_2SO_4 in 45 mL of water and stir the mixture. Slowly add (dropwise) a solution of 2.55 g (40 mmol) of $NaNO_2$ in 75 mL of water and stir at 0°-5°C for 0.5 hours. Add a boiling solution of 35.1 g $CuSO_4$ in 135 mL of water and heat at 100°C for 15 min. Cool the mixture, extract with CH_2Cl_2 (2 X 200 mL), wash the extracts with brine, dry over $MgSO_4$, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 1.5%-10% MeOH/ CH_2Cl_2) to give 11.36 g of the product compound.

Step B:



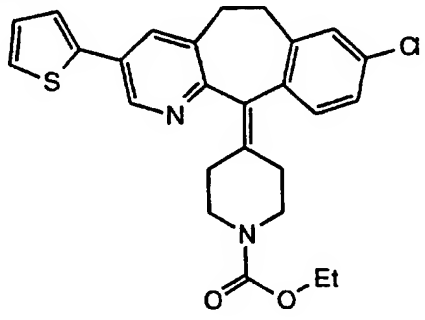
Combine 11.36 g (28.5 mmol) of the Product of Step A and 12.4 g (34.7 mmol) of N-phenyltriflimide in 120 mL of dry CH_2Cl_2 at 0°C, add 4.6 mL (33 mmol) of Et_3N and stir at 25°C overnight. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%-5% EtOAc/ CH_2Cl_2) to give 10.95 g of the product compound. Recrystallize from hot MeOH. m.p. = 154.5°-156°C; Mass Spec.: (FAB) MH^+ = 531

Step C:



Combine 12.2 g (23 mmol) of the Product of Step B and 85 mL of 1-methyl-2-pyrrolidinone at 25°C, then add 2.84 g LiCl, 0.212 g of tris-furylphosphine and 0.585 g of dipalladiumtribenzylideneacetone and stir for 15 min. Slowly add (dropwise) 7.5 mL (25.77 mmol) of tributylvinyltin and stir at 25°C for 2.5 hours. Dilute with 500 mL of water at 0°C and extract with 6700 mL of EtOAc. Filter the organic phase through celite®, wash the celite with EtOAc, then wash the filtrate twice with 30% NaF (aqueous). Filter the organic solution, wash with brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 15%-40% EtOAc/hexane) to give 8.58 g of the product compound. Mass Spec.: (FAB) $MH^+ = 409$

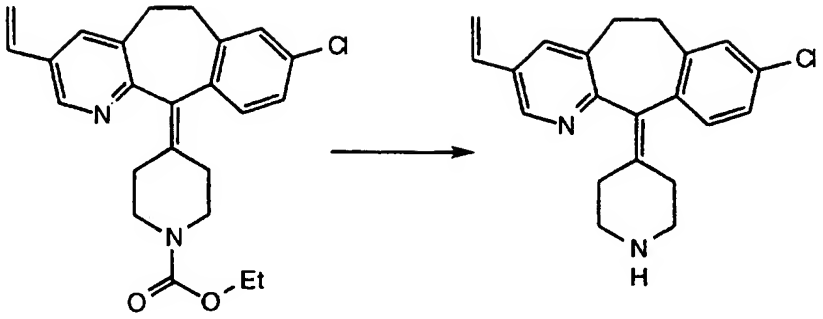
Using 2-(tributylstannyl)thiophene and the compound of Preparative Example 70, Step B, and following substantially the same procedure as described for Preparative Example 70, Step C, the compound:



(Preparative Example 70-A)

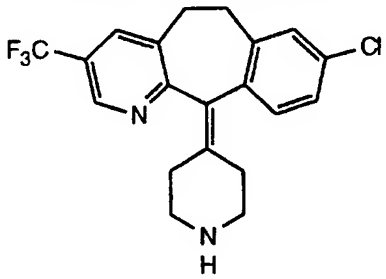
was prepared. m.p. = 155°~157°C, Mass Spec.: $MH^+ = 465$.

Step D:

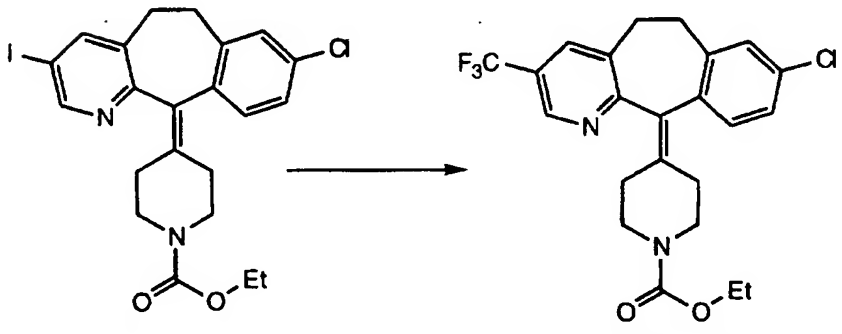


Hydrolyze 1.18 g (2.89 mmol) of the product of Step C via substantially the same procedure as described in Example 358, Step A, of WO 95/10516 ,to give 0.95 g of the product compound. Mass Spec.: (FAB) MH^+ = 337

PREPARATIVE EXAMPLE 71

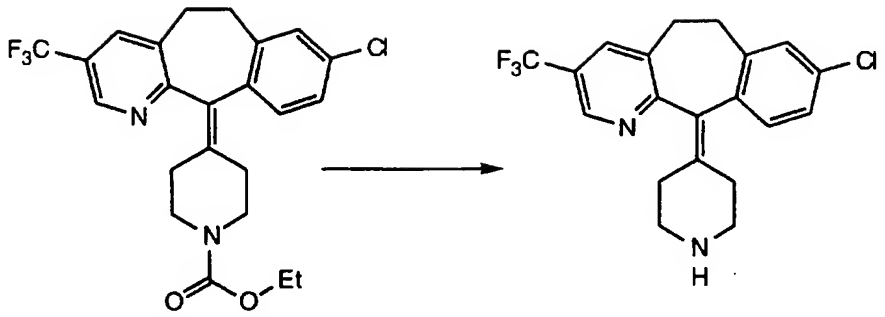


Step A:



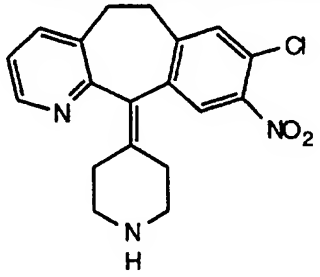
Combine 1.01 g (19.9 mmol) of the Product of Preparative Example 48, Step A, 30 mL of DMF, 1.33 g (6.96 mmol) of methyl 2,2-difluoro-2-(fluorosulfonyl)-acetate and 0.75 g (3.97 g) of CuI. Heat the mixture at 60°-80°C for 3 hours, then concentrate to a residue. Dilute the residue with water, extract with CH_2Cl_2, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 30% EtOAc/hexane, then 10% MeOH/CH_2Cl_2 + NH_4OH) to give 0.15 g of the product compound. Mass Spec.: MH^+ = 451.1

Step B:

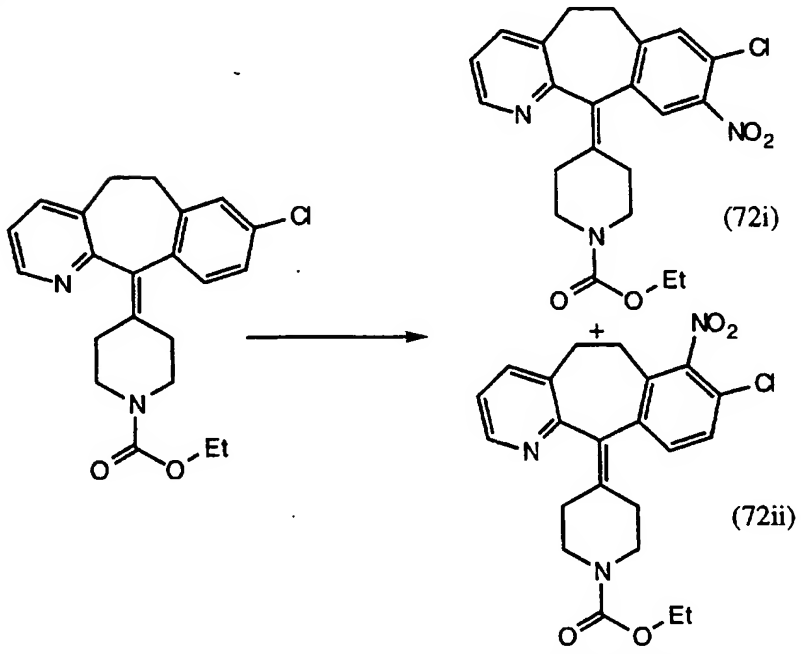


Hydrolyze the product of Step A using essentially the same procedure as described in Preparative Example 1, Step G, of WO 95/10516, to give the product compound. Mass Spec.: $MH^+ = 379$

PREPARATIVE EXAMPLE 72



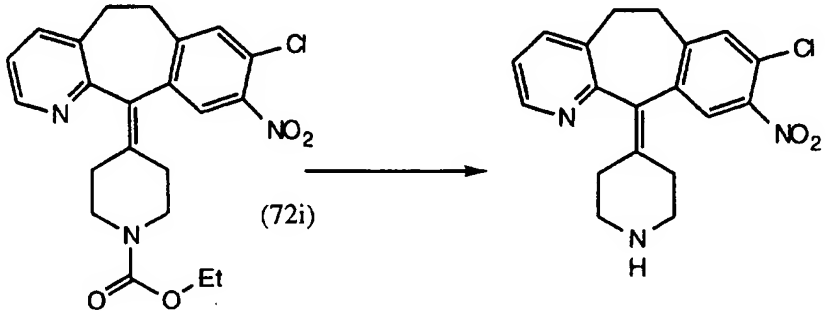
Step A:



Dissolve 20 g (50 mmol) of the Product of Preparative Example 1, Step F, of WO 95/10516, in 400 mL of concentrated H_2SO_4, cool to -5°C and add 5.1 g (50 mmol) of KNO_3 in small portions. Stir for 3 hours, cool

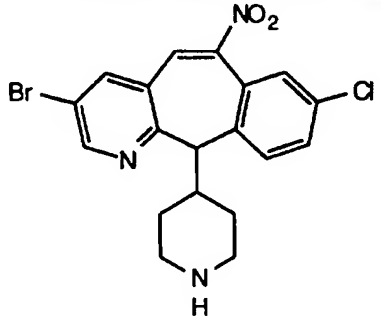
the mixture and slowly basify with 50% NaOH (aqueous). Extract with CH_2Cl_2 (3 X 500 mL), dry the combined extracts over $MgSO_4$, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 50% EtOAc/hexane) to give 16.33 g of the product compound (72i) and 2.6 g of the product compound (72ii). Mass Spec. (72(i) and (72(ii)): MH^+ = 428

Step B:

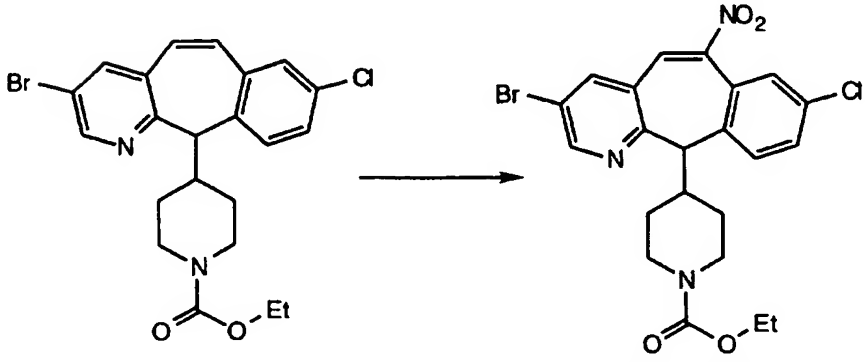


Hydrolyze 5.46 g (12.76 mmol) of the Product of (72i) from Step A, via substantially the same procdure as described for Example 358, Step A, of WO 95/10516, to give 4.34 g of the product compound. Mass Spec.: MH^+ = 356

PREPARATIVE EXAMPLE 73



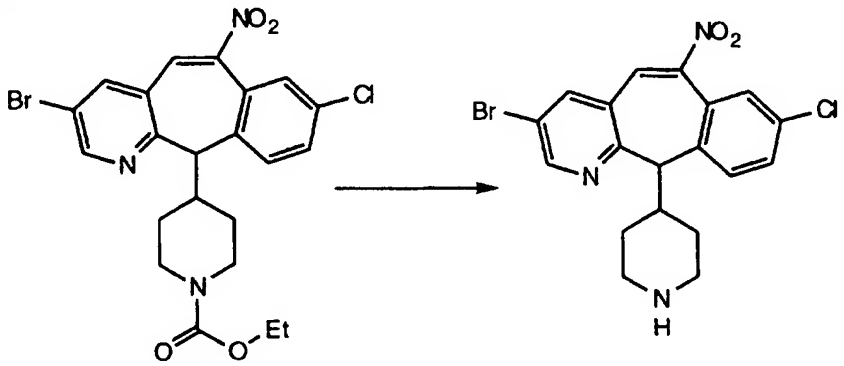
Step A:



Combine 1.6 g of the Product (54i) of Preparative Example 54, Step B, 12 mL of CH_2Cl_2, and 1.16 g of tetrabutylammonium nitrate, cool to 0°C

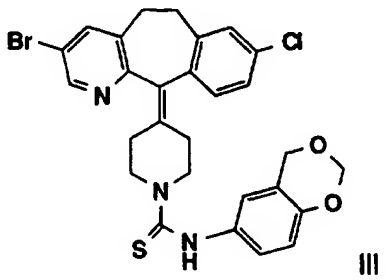
and slowly add (dropwise) a solution of 0.8 g of TFAA in 2 mL of CH_2Cl_2. Stir for 6 hours at 0°C, let the mixture stand at 0°C overnight, then wash successively with saturated $NaHCO_3$ (aqueous), water and brine, and dry over Na_2SO_4. Concentrate *in vacuo* to a residue, then chromatograph (silica gel, 30% EtOAc/hexane) to give 0.38 g of the product compound.

Step B:



Hydrolyze 0.38 g of the Product of Step A via substantially the same procedure as described for Example 358, Step A, of WO 95/10516, to give 0.235 g of the product compound.

Preparative Example 75. 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-N-(4H-1,3-benzodioxin-6-yl)-1-piperidinecarbothioamide



III

Dissolve 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5.6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine (0.5 gm, 1.61 mmol) in 5 mL of dry tetrahydrofuran. Add 4H-1,3-benzodioxin-6-yl) isothiocyanate (0.34 gm, 1.77 mmol) and stir at ambient temperature for 24 hours. Evaporate the reaction mixture to an oil and chromatograph on silica gel using 1% up to 5% methanol/methylene chloride as the eluent to obtain 0.893 g of title compound. FABMS M+1= 694

ASSAYS

1. In vitro enzyme assays: FPT IC_{50} (inhibition of farnesyl protein transferase, in vitro enzyme assay) are determined by the methods disclosed in WO/10515 or WO 95/10516. The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent (IC_{50} <10 μM) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

2. Cell-based assay. COS IC_{50} values refer to the COS cells activity inhibition of Ras processing, are determined by the methods disclosed in WO/10515 or WO 95/10516.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or

parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A-Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B-Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

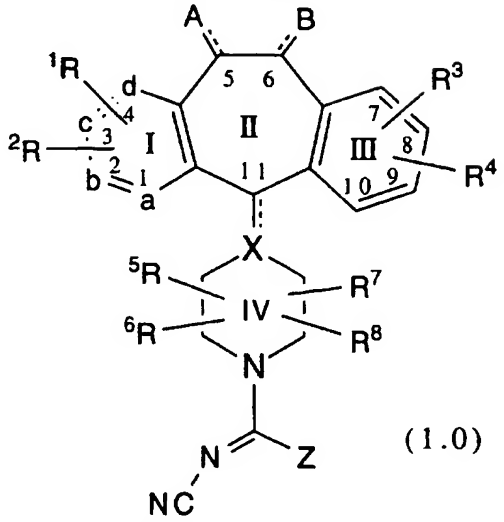
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2; each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$ (e.g., $-OCH_3$), $-COR^{10}$, $-SR^{10}$ (e.g., $-SCH_3$ and $-SCH_2C_6H_5$), $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2, e.g., $-SOCH_3$ and $-SO_2CH_3$), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{11}N(R^{75})_2$ wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$ (e.g., $-S(CH_2)_2NHC(O)O$-t-butyl and $-S(CH_2)_2NH_2$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$,

$-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} and R^{12} independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, aryl, aralkyl or $-NR^{40}R^{42}$ wherein R^{40} and R^{42} independently represent H, aryl, alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl;

R^{11} represents alkyl or aryl;

X represents N, CH or C, such that when X is N or CH, there is a single bond to carbon atom 11 as represented by the solid line; or when X is C, there is a double bond to carbon atom 11, as represented by the solid and dotted lines;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-NO_2$, $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, oxy, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4; and

Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, $-OR^{40}$, $-SR^{40}$, $-CR^{40}R^{42}$ or $-NR^{40}R^{42}$ wherein R^{40} and R^{42} are defined hereinbefore.

Preferably in compound (1.0), there is a single bond at carbon atom 11, X is carbon, positions 3, 8 and 10 are substituted on the ring, preferably with halo; and Z is $-NHR^{40}$, preferably where R^{40} is heteroarylalkyl, more preferably 3 or 4-methyl pyridyl N-oxide.

2. The compound of claim 1 wherein a is N, and R^1 is H; R^2, R^3 and R^4 are halo; X is CH; and R^5, R^6, R^7 and R^8 are hydrogen.

3. The compound of claim 2 wherein Z is $-NR^{40}R^{42}$.

4. The compound of claim 3 wherein R^{40} is H and R^{42} is heteroarylalkyl.

5. The compound of claim 4 wherein R^{42} is 2-, 3- or 4-pyridylmethyl N-oxide.

6. The compound of claim 1 selected from any of Examples 1-83.

7. The compound of claim 1 selected from Example 9.

8. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

9. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of claim 1.

10. The method of Claim 9 wherein the the cells inhibited are tumor cells expressing an activated ras oncogene.

11. The method of Claim 9 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

12. The method of Claim 9 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of ras farnesyl protein transferase.

13. The method of Claim 9 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

INTERNATIONAL SEARCH REPORT

Intern. .al Application No
PCT/US 97/12923

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 C07D401/14 C07D405/14 C07D405/12 C07D401/12
A61K31/445 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 10516 A (SCHERING CORPORATION) 20 April 1995 see claims ---	1,8-13
Y	WO 95 10515 A (SCHERING CORPORATION) 20 April 1995 see claims ---	1,8-13
A	EP 0 341 860 A (SCHERING CORPORATION) 15 November 1989 see claims ---	1-13
A	EP 0 270 818 A (SCHERING CORPORATION) 15 June 1988 see claims -----	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1997	0 4. 11. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/US 97/ 12923

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos..
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 9-13
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern ial Application No
PCT/US 97/12923

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9510516 A	20-04-95	AU 7970394 A	04-05-95
		CA 2174104 A	20-04-95
		EP 0723540 A	31-07-96
		HU 76056 A	30-06-97
		JP 8510760 T	12-11-96
		ZA 9407971 A	12-07-96
WO 9510515 A	20-04-95	AU 7930994 A	04-05-95
		CA 2174105 A	20-04-95
		EP 0723538 A	31-07-96
		HU 76066 A	30-06-97
		JP 8510759 T	12-11-96
		ZA 9407970 A	12-07-96
EP 0341860 A	15-11-89	AT 108453 T	15-07-94
		AU 629835 B	15-10-92
		AU 3734489 A	24-11-89
		DE 68916699 D	18-08-94
		DE 68916699 T	01-12-94
		DK 256890 A	21-12-90
		EP 0411048 A	06-02-91
		ES 2056214 T	01-10-94
		FI 96690 B	30-04-96
		IE 64522 B	09-08-95
		IL 90101 A	14-11-96
		JP 6078315 B	05-10-94
		JP 3504012 T	05-09-91
		KR 9504004 B	22-04-95
		NO 175480 B	11-07-94
		OA 9629 A	30-04-93
		WO 8910369 A	02-11-89
		US 5104876 A	14-04-92
EP 0270818 A	15-06-88	US 4826853 A	02-05-89
		AT 116310 T	15-01-95
		AU 635400 B	18-03-93
		AU 7285991 A	30-05-91
		AU 604285 B	13-12-90
		AU 8336287 A	25-05-88
		CA 1305147 A	14-07-92

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/US 97/12923

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0270818 A		CA 1321589 A	24-08-93
		CS 9104143 A	16-09-92
		DE 3750929 D	09-02-95
		DE 3750929 T	01-06-95
		DK 73193 A	21-06-93
		DK 354688 A	28-06-88
		EP 0330673 A	06-09-89
		EP 0685476 A	06-12-95
		ES 2068179 T	16-04-95
		FI 96768 B	15-05-96
		HK 186396 A	11-10-96
		IE 65174 B	04-10-95
		JP 6078316 B	05-10-94
		JP 2500910 T	29-03-90
		OA 9546 A	31-01-93
		WO 8803138 A	05-05-88
		US 5089496 A	18-02-92
		US 5665726 A	09-09-97
		US 5438062 A	01-08-95
		ZA 8708128 A	29-04-88